```
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PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2


* * * * * * * * * *   Welcome to STN International   * * * * * * * * * *

 NEWS  1          Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2          "Ask CAS" for self-help around the clock
 NEWS  3  JUL 20  Powerful new interactive analysis and visualization software,
                  STN AnaVist, now available
 NEWS  4  AUG 11  STN AnaVist workshops to be held in North America
 NEWS  5  AUG 30  CA/CAplus -Increased access to 19th century research documents
 NEWS  6  AUG 30  CASREACT - Enhanced with displayable reaction conditions
 NEWS  7  SEP 09  ACD predicted properties enhanced in REGISTRY/ZREGISTRY
 NEWS  8  OCT 03  MATHDI removed from STN
 NEWS  9  OCT 04  CA/CAplus-Canadian Intellectual Property Office (CIPO) added
                  to core patent offices
 NEWS 10  OCT 06  STN AnaVist workshops to be held in North America
 NEWS 11  OCT 13  New CAS Information Use Policies Effective October 17, 2005
 NEWS 12  OCT 17  STN(R) AnaVist(TM), Version 1.01, allows the export/download
                  of CAplus documents for use in third-party analysis and
                  visualization tools
 NEWS 13  OCT 27  Free KWIC format extended in full-text databases
 NEWS 14  OCT 27  DIOGENES content streamlined
 NEWS 15  OCT 27  EPFULL enhanced with additional content

 NEWS EXPRESS  JUNE 13 CURRENT WINDOWS VERSION IS V8.0, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 13 JUNE 2005

 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
 NEWS INTER    General Internet Information
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 NEWS PHONE    Direct Dial and Telecommunication Network Access to STN
 NEWS WWW      CAS World Wide Web Site (general information)

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  * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 13:47:27 ON 29 OCT 2005

=> fil reg
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.63       0.63
```

FILE 'REGISTRY' ENTERED AT 13:49:07 ON 29 OCT 2005
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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES: 27 OCT 2005 HIGHEST RN 866318-76-5
DICTIONARY FILE UPDATES: 27 OCT 2005 HIGHEST RN 866318-76-5

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

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conducting SmartSELECT searches.

```
**********************************************************************
*                                                                    *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,    *
* effective March 20, 2005.  A new display format, IDERL, is now     *
* available and contains the CA role and document type information.  *
*                                                                    *
**********************************************************************
```

Structure search iteration limits have been increased. See HELP SLIMITS
for details.

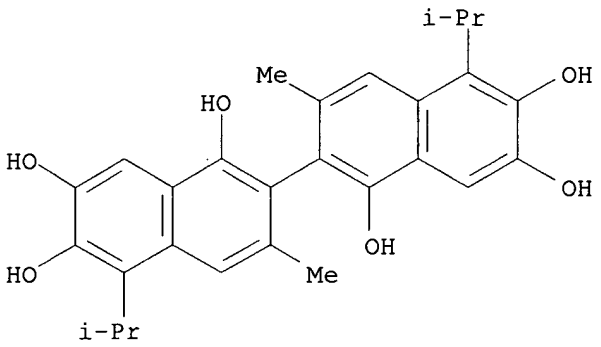
REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document. For information
on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

```
=> s apogossypol/cn
L1            1 APOGOSSYPOL/CN

=> d

L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   66389-74-0  REGISTRY
ED   Entered STN:  16 Nov 1984
CN   [2,2'-Binaphthalene]-1,1',6,6',7,7'-hexol, 3,3'-dimethyl-5,5'-bis(1-
     methylethyl)-, (2S)- (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   Apogossypol
MF   C28 H30 O6
LC   STN Files:   BEILSTEIN*, BIOSIS, CA, CAPLUS, CASREACT, DDFU, DRUGU,
       NAPRALERT, TOXCENTER, USPATFULL
         (*File contains numerically searchable property data)
```



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

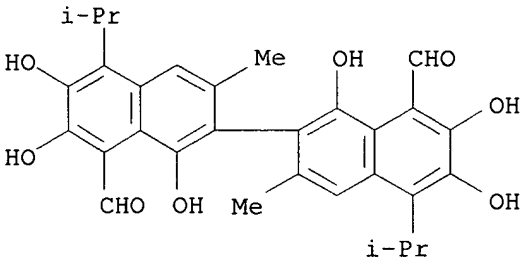
19 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
19 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> s gossypol/cn
L2 1 GOSSYPOL/CN

=> d

L2 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2005 ACS on STN
RN 303-45-7 REGISTRY
ED Entered STN: 16 Nov 1984
CN [2,2'-Binaphthalene]-8,8'-dicarboxaldehyde, 1,1',6,6',7,7'-hexahydroxy-3,3'-dimethyl-5,5'-bis(1-methylethyl)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN [2,2'-Binaphthalene]-8,8'-dicarboxaldehyde, 1,1',6,6',7,7'-hexahydroxy-5,5'-diisopropyl-3,3'-dimethyl- (8CI)
OTHER NAMES:
CN (±)-Gossypol
CN 1,1',6,6',7,7'-Hexahydroxy-3,3'-dimethyl-5,5'-diisopropyl-2,2'-binaphthyl-8,8'-dialdehyde
CN 1,1',6,6',7,7'-Hexahydroxy-3,3'-dimethyl-5,5'-diisopropyl[2,2'-binaphthalene]-8,8'-dicarboxaldehyde
CN 1,1',6,6',7,7'-Hexahydroxy-5,5'-diisopropyl-3,3'-dimethyl-2,2'-binaphthalene-8,8'-dicarboxaldehyde
CN 1,6,7,1',6',7'-Hexahydroxy-5,5'-diisopropyl-3,3'-dimethyl-[2,2']binaphthalenyl-8,8'-dicarboxaldehyde
CN 2,2'-Bis[1,6,7-trihydroxy-3-methyl-5-isopropyl-8-aldehydonaphthyl]
CN 2,2'-Bis[8-formyl-1,6,7-trihydroxy-5-isopropyl-3-methylnaphthyl]
CN **Gossypol**
CN No Fertil
CN NSC 56817
CN NSC 624336
CN Pogosin
CN Tash 1
FS 3D CONCORD
DR 732279-01-5, 40112-23-0
MF C30 H30 O8
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CIN, CSCHEM, DDFU, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IMSDRUGNEWS, IMSRESEARCH, IPA, MEDLINE, MRCK*, NAPRALERT, NIOSHTIC, PROMT, PROUSDDR, RTECS*, SPECINFO,

SYNTHLINE, TOXCENTER, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)



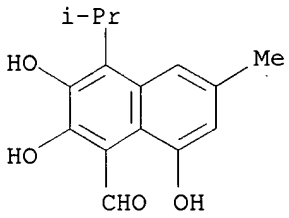
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2606 REFERENCES IN FILE CA (1907 TO DATE)
173 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
2606 REFERENCES IN FILE CAPLUS (1907 TO DATE)
21 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=> s hemigossypol/cn
L3 1 HEMIGOSSYPOL/CN

=> d

L3 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2005 ACS on STN
RN 40817-07-0 REGISTRY
ED Entered STN: 16 Nov 1984
CN 1-Naphthalenecarboxaldehyde, 2,3,8-trihydroxy-6-methyl-4-(1-methylethyl)-(9CI) (CA INDEX NAME)
OTHER NAMES:
CN **Hemigossypol**
CN Isohemigossypol
FS 3D CONCORD
MF C15 H16 O4
CI COM
LC STN Files: AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CHEMINFORMRX, IPA, NAPRALERT, SPECINFO, TOXCENTER
(*File contains numerically searchable property data)



PROPERTY DATA AVAILABLE IN THE !PROP' FORMAT

63 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
63 REFERENCES IN FILE CAPLUS (1907 TO DATE)

```
=> sel rn name l1
E1 THROUGH E2 ASSIGNED

=> sel rn name l3
E3 THROUGH E5 ASSIGNED

=> fil medl capl biosis uspatf wpids
COST IN U.S. DOLLARS                        SINCE FILE      TOTAL
                                               ENTRY    SESSION
FULL ESTIMATED COST                            20.96      21.59

FILE 'MEDLINE' ENTERED AT 13:50:20 ON 29 OCT 2005

FILE 'CAPLUS' ENTERED AT 13:50:20 ON 29 OCT 2005
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FILE 'USPATFULL' ENTERED AT 13:50:20 ON 29 OCT 2005
CA INDEXING COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'WPIDS' ENTERED AT 13:50:20 ON 29 OCT 2005
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=> s e1-2
L4          76 (APOGOSSYPOL/BI OR 66389-74-0/BI)

=> s e3-5
L5         153 (HEMIGOSSYPOL/BI OR ISOHEMIGOSSYPOL/BI OR 40817-07-0/BI)

=> s cancer or carcinoma or proliferat?
L6     2737782 CANCER OR CARCINOMA OR PROLIFERAT?

=> s l4 and l6
L7          16 L4 AND L6

=> dup rem l7
PROCESSING COMPLETED FOR L7
L8           10 DUP REM L7 (6 DUPLICATES REMOVED)

=> d ibib abs 9-10

L8   ANSWER 9 OF 10     MEDLINE on STN                  DUPLICATE 4
ACCESSION NUMBER:   2003213689     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 12457630
TITLE:              An in vitro study of inhibitory activity of gossypol, a
                    cottonseed extract, in human carcinoma cell
                    lines.
AUTHOR:             Le Blanc Michael; Russo Jennifer; Kudelka Andrzej P; Smith
                    Judith A
CORPORATE SOURCE:   University of Houston College of Pharmacy, Houston, TX,
                    USA.
SOURCE:             Pharmacological research : official journal of the Italian
                    Pharmacological Society, (2002 Dec) 46 (6) 551-5.
                    Journal code: 8907422. ISSN: 1043-6618.
PUB. COUNTRY:       England: United Kingdom
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        200305
```

ENTRY DATE: Entered STN: 20030509
Last Updated on STN: 20030528
Entered Medline: 20030527

AB Gossypol, a cottonseed extract, has been shown to have antiproliferative activity in a variety of **cancer** cell lines. The objective of this study was to determine the inhibitory effects of gossypol on cell **proliferation**. Five human **carcinoma** cell lines were evaluated including endometrial (RL95-2), ovarian (SKOV-3), medullary thyroid (TT), and adrenocortical (NCI-H295R and SW-13). Gossypol and the metabolite, **apogossypol** hexaacetate, were examined at concentrations up to 500 microg ml(-1) and the IC(50) was determined using the MTT assay. Gossypol and **apogossypol** hexaacetate produced a dose-dependent growth inhibition in all cellular lines examined. The IC(50) for gossypol ranged from 1.3 to 18.9 microM while the IC(50) for **apogossypol** hexaacetate ranged from 5.2 to 9.0 microM. The results indicate that gossypol possesses antiproliferative action toward human **carcinoma** cells in vitro. These investigations suggest that gossypol may have therapeutic potential for the treatment of **cancer**.

L8 ANSWER 10 OF 10 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2000:261971 BIOSIS
DOCUMENT NUMBER: PREV200000261971
TITLE: Structure-activity studies on gossypol in tumor cell lines.
AUTHOR(S): Shelley, Michael D. [Reprint author]; Hartley, Laura; Groundwater, Paul W.; Fish, Reginald G.
CORPORATE SOURCE: Research Laboratories, Velindre NHS Trust, Whitchurch, Cardiff, CF14 2TL, UK
SOURCE: Anti-Cancer Drugs, (March, 2000) Vol. 11, No. 3, pp. 209-216. print.
CODEN: ANTDEV. ISSN: 0959-4973.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 21 Jun 2000
Last Updated on STN: 5 Jan 2002

AB Gossypol ((2,2'-binaphthalene)-8,8'-dicarboxaldehyde-1,1',6,6',7,7'-hexahydroxy-5,5'-diisopropyl-3,3'-dimethyl) 1a is a naturally occurring compound extracted from the cotton plant and has been extensively studied as an oral male contraceptive. Its favorable toxicity profile, and the more recent demonstration of anti-tumor activity in animals and humans, prompted us to investigate the role of the aldehyde groups in a structure-activity study in cultured tumor cells. Four racemic compounds were evaluated: gossypol 1a, gossypolone 2, the bis Schiff's base of L-phenylalanine methyl ester with gossypol (bis Schiff's base) 1c and **apogossypol** 1b. The former two compounds both retain the aldehyde functional groups at positions 8 and 8' of the molecule whilst in the latter two compounds the aldehydes are blocked or absent, respectively. In addition, the I- and d-isomers of gossypol 1a, the bis Schiff's base 1c and the half Schiff's base 1d (one aldehyde blocked) were tested. The cell lines studied included melanoma (SK-mel-19), cervix (Sihas), small cell lung (H69) and myelogenous leukemia (K562). Cytotoxicity was measured using the MTT and flow cytometric viability assays. Racemic gossypol 1a and gossypolone 2 induced similar dose-dependent decreases in cell viability in all the cell lines with IC50 values of 23-46 and 28-50 muM, respectively. In contrast, the racemic bis Schiff's base derivative of gossypol 1c and **apogossypol** 1b showed minimal activity in any cell line up to 50 muM. The I-enantiomer of gossypol 1a was significantly more active than the d-enantiomer (IC50 of 20 versus >50 muM, respectively). When one aldehyde of either enantiomer was blocked 1d cytoxicity was comparable to the I-enantiomer of gossypol. The data suggest that only one aldehyde group is required for the cytotoxicity of gossypol 1a, irrespective of the stereo-configuration

```
=> s l5 and l6
L9           2 L5 AND L6

=> dup rem l9
PROCESSING COMPLETED FOR L9
L10          2 DUP REM L9 (0 DUPLICATES REMOVED)

=> d ibib abs tot

L10  ANSWER 1 OF 2  USPATFULL on STN
ACCESSION NUMBER:        2005:262008  USPATFULL
TITLE:                   11-Beta hydroxysteroid dehydrogenase type 1 inhibitors
                         as anti-obesity/anti-diabetes compounds and 17-beta
                         hydrosteroid dehydrogenase type I inhibitors as useful
                         agents for the treatment of cancers,
                         especially breast cancer
INVENTOR(S):             Vander Jagt, David L., Albuquerque, NM, UNITED STATES
                         Royer, Robert E., Albuquerque, NM, UNITED STATES
                         Deck, Lorraine M., Albuquerque, NM, UNITED STATES

                              NUMBER         KIND    DATE
                         ---------------- ------ --------
PATENT INFORMATION:      US 2005228038      A1   20051013
APPLICATION INFO.:       US 2005-93493      A1   20050330  (11)

                                NUMBER         DATE
                         ------------------ --------
PRIORITY INFORMATION:    US 2004-560387P    20040408 (60)
DOCUMENT TYPE:           Utility
FILE SEGMENT:            APPLICATION
LEGAL REPRESENTATIVE:    Henry D. Coleman, 714 Colorado Avenue, Bridgeport, CT,
                         06605, US
NUMBER OF CLAIMS:        25
EXEMPLARY CLAIM:         1
LINE COUNT:              901
AB     This invention is directed to the discovery that 11-Beta Hydroxysteroid
       Dehydrogenase Type 1 may be a common molecular etiology for visceral
       obesity and the metabolic syndrome of obesity as well a treatment for
       diabetes, especially type II diabetes. The present invention also
       relates to the use of certain compounds as inhibitors of 17-Beta
       Hydroxysteroid Dehydrogenase Type 1 and their use for the treatment of
       cancer, especially breast cancer.


L10  ANSWER 2 OF 2  CAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:        1986:106480  CAPLUS
DOCUMENT NUMBER:         104:106480
TITLE:                   Interaction of cotton tissue culture cells and
                         Verticillium dahliae
AUTHOR(S):               Altman, David W.; Stipanovic, Robert D.; Mitten, Donna
                         M.; Heinstein, Peter
CORPORATE SOURCE:        Natl. Cotton Pathol. Res. Lab., USDA, College Station,
                         TX, 77841, USA
SOURCE:                  In Vitro Cellular & Developmental Biology (1985),
                         21(12), 659-64
                         CODEN: ICDBEO; ISSN: 0883-8364
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   Elicitation of sesquiterpenoid aldehyde phytoalexins in Gossypium arboreum
     cell suspension cultures was confirmed by TLC, HPLC, and an
     aniline-reaction assay after inoculation with heat-treated conidia of V.
```

dahliae. A 2.3-fold mean increase in total terpenoids was observed Component phytoalexins varied, with either **hemigossypol** and gossypol being detected or the O-methylated terpenoids **hemigossypol**-6-Me ether and related compds. Long-term Gossypium suspension cultures were mixoploid with an increase in chromosome no. and mean DNA content. Addn. of V. dahliae elicitor(s) to the medium for embryo-**proliferating** callus of G. hirsutum inhibited growth and embryo prodn. with a linear correlation between the elicitor concn. and the no. of embryos. Addn. of 14C-labeled NaOAc to suspension cells gave 30% incorporation, and from 13C-NaOAc addn., labeled sesquiterpenoid aldehydes were recovered. The cotton-Verticillium system is another case of secondary metabolite elicitation in plant tissue culture and might be used for basic studies of host-pathogen interaction as well as for a selection tool to obtain resistance to an important disease.

=> fil reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	29.09	50.68

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-0.73	-0.73

FILE 'REGISTRY' ENTERED AT 13:53:32 ON 29 OCT 2005

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 27 OCT 2005 HIGHEST RN 866318-76-5
DICTIONARY FILE UPDATES: 27 OCT 2005 HIGHEST RN 866318-76-5

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TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

Please note that search-term pricing does apply when conducting SmartSELECT searches.

****
* *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
* *
****

Structure search iteration limits have been increased. See HELP SLIMITS for details.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

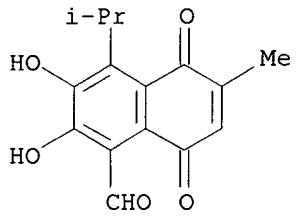
http://www.cas.org/ONLINE/UG/regprops.html

=> s hemigossypolone/cn

L11 1 HEMIGOSSYPOLONE/CN

=> d

L11 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2005 ACS on STN
RN 35688-47-2 REGISTRY
ED Entered STN: 16 Nov 1984
CN 1-Naphthalenecarboxaldehyde, 5,8-dihydro-2,3-dihydroxy-6-methyl-4-(1-methylethyl)-5,8-dioxo- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **Hemigossypolone**
CN NSC 650936
CN p-Hemigossypolone
MF C15 H14 O5
CI COM
LC STN Files: AGRICOLA, BEILSTEIN*, BIOSIS, CA, CAPLUS, NAPRALERT, SPECINFO, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

38 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
38 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> sel rn name l11
E6 THROUGH E9 ASSIGNED

=> FIL MEDL CAPL BIOSIS USPATF WPIDS

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	7.26	57.94

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-0.73

FILE 'MEDLINE' ENTERED AT 13:53:54 ON 29 OCT 2005

FILE 'CAPLUS' ENTERED AT 13:53:54 ON 29 OCT 2005
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FILE 'BIOSIS' ENTERED AT 13:53:54 ON 29 OCT 2005

FILE 'USPATFULL' ENTERED AT 13:53:54 ON 29 OCT 2005

FILE 'WPIDS' ENTERED AT 13:53:54 ON 29 OCT 2005
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=> s e6-9
L12 73 (HEMIGOSSYPOLONE/BI OR "NSC 650936"/BI OR P-HEMIGOSSYPOLONE/BI OR 35688-47-2/BI)

=> s l12 and l6
L13 6 L12 AND L6

=> dup rem l13
PROCESSING COMPLETED FOR L13
L14 4 DUP REM L13 (2 DUPLICATES REMOVED)

=> d ibib abs tot

L14 ANSWER 1 OF 4 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2005-564053 [57] WPIDS
CROSS REFERENCE: 2003-140460 [13]
DOC. NO. CPI: C2005-170457
TITLE: Treating, ameliorating or preventing hyperproliferative disease e.g., **cancer** in subject, involves administering gossypol compound and anticancer agent to subject, or administering gossypol compound and subjecting subject to radiation.
DERWENT CLASS: B04 B05
INVENTOR(S): WANG, S; YANG, D
PATENT ASSIGNEE(S): (GEOU) UNIV GEORGETOWN MEDICAL CENT; (UNMI) UNIV MICHIGAN
COUNTRY COUNT: 108
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2005069771	A2	20050804	(200557)*	EN	262

RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2005069771	A2	WO 2004-US40553	20041206

PRIORITY APPLN. INFO: US 2003-729156 20031205
AN 2005-564053 [57] WPIDS
CR 2003-140460 [13]
AB WO2005069771 A UPAB: 20050907
NOVELTY - Treating, ameliorating or preventing (M1) a hyperproliferative disease in a subject, involves administering to the subject a gossypol compound and one or more second agent chosen from an anticancer agent and radiation, where the combination of (plus or minus)-gossypol, heat, and radiation is not administered.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) a pharmaceutical composition (PC) comprising a gossypol compound and one or more anticancer agents; and

(2) a kit comprising a gossypol compound, one or more anticancer agents, and instructions for administering the gossypol compound and the anticancer agents to a subject.

ACTIVITY - Cytostatic; Anti-HIV; Vasotropic; Antiinflammatory; Antibacterial; Fungicide; Virucide.

MECHANISM OF ACTION - Antagonist of Bcl-2 family proteins; Induces apoptosis; Inhibits cell **proliferation**. In vivo analysis of gossypol compounds in combination with radiation therapy in inhibiting cell **proliferation** was carried out in PC-3 xenograft mouse model as follows. The xenograft mice (25) were divided into 5 groups. Group 1 (vehicle control) mice were orally administered with alcohol (10%), daily, Group 2 (radiation only) mice were subjected to radiation (2 Gy) 5 times/week for 2 weeks and orally administered daily with alcohol (10%), Group 3 (radiation plus gossypol) mice were subjected to radiation (2 Gy) 5 times/week for 3 weeks and orally administered daily with (-)-gossypol (10 mg/kg) every day for 4 weeks, Group 4 (gossypol only) mice were orally administered daily with (-)-gossypol (10 mg/kg) every day for 4 weeks, and Group 5 (control) mice were not subjected to treatment. During the treatment course, tumor sizes and animal weights were measured 3 times per/week for each animal. Treatment with (-)-gossypol alone or with radiation therapy alone had minimal antitumor effect. Results showed that there was more than 90% inhibition in tumor cell growth in animals receiving radiation therapy in combination with gossypol as compared to the group controls.

USE - (M1) is useful for treating, ameliorating or preventing a hyperproliferative disease in a subject, where the subject is a human. The disease is neoplastic disease. The hyperproliferative disease is **cancer**, preferably breast **cancer**, prostate **cancer**, pancreatic **cancer**, colon **cancer**, lung **cancer**, lymphoma, melanoma or head-neck **cancer**. The **cancer** is metastatic or is a tumor, where the treatment or amelioration results in regression of the tumor. The hyperproliferative disease is associated with overexpression of a Bcl-2 family member protein, where the Bcl-2 family protein is Bcl-2, Bcl-XL, Mcl-1, A1/BFL-1, BOO-DIVA, Bcl-w, Bcl-6, Bcl-8 or Bcl-y. The **cancer** is resistant to anticancer agent or radiation therapy (all claimed). PC is useful for treating hyperproliferative disease, tumor such as Wilm's tumor, metastatic **cancer**, cervical **carcinoma**, testicular **carcinoma**, genitourinary **carcinoma**, thyroid **carcinoma**, Hodgkin's disease, non-Hodgkin's sarcoma, etc. PC is useful for treating infections (e.g., bacterial, viral, fungal and mycoplasma infections), AIDS, inflammatory disease, vascular diseases, etc. PC is useful for preventing the onset or spread of neoplastic disease, for treating diseased cells, tissues, organs or pathological conditions and/or disease states in a subject, and for modulating cell division in a tissue.

ADVANTAGE - PC is less toxic and more tolerable.

DESCRIPTION OF DRAWING(S) - The figure is a graph representing the tumor size in PC-3 xenograft model mice subjected to radiation and/or gossypol treatments.

Dwg.36/46

L14 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 1

ACCESSION NUMBER:	2004:907153 CAPLUS
DOCUMENT NUMBER:	141:388644
TITLE:	Gossypol compound antagonists of Bcl-2 family proteins, and use with with other therapeutic means in the treatment of neoplastic and other diseases
INVENTOR(S):	Wang, Shaomeng; Yang, Dajun
PATENT ASSIGNEE(S):	The Regents of the University of Michigan, USA; Georgetown University
SOURCE:	U.S. Pat. Appl. Publ., 143 pp., Cont.-in-part of U.S. Ser. No. 158,769.

CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004214902	A1	20041028	US 2003-729156	20031205
WO 2002097053	A2	20021205	WO 2002-US17206	20020530
WO 2002097053	A3	20040910		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2003008924	A1	20030109	US 2002-158769	20020530
WO 2005069771	A2	20050804	WO 2004-US40553	20041206

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:		
US 2001-293983P	P	20010530
US 2002-158769	A2	20020530
WO 2002-US17206	A2	20020530
US 2003-729156	A	20031205

AB The invention relates to naturally occurring and chemical synthesized small mol. antagonists of Bcl-2 family proteins. In particular, the invention provides gossypol compds. (e.g., isomers, enantiomers, racemic compds., metabolites, derivs., pharmaceutically acceptable salts, in combination with acids or bases, and the like) and methods of using these compds. as antagonists of the anti-apoptotic effects of Bcl-2 family member proteins (e.g., Bcl-2, Bcl-XL, and the like). The invention also provides compns. comprising gossypol compds. and optionally one or more addnl. therapeutic agents (e.g., anticancer/chemotherapeutic agents). The invention also provides methods for treating diseases and pathologies (e.g., neoplastic diseases) comprising administering a composition comprising gossypol compds. and optionally one or more addnl. therapeutic agents (e.g., anticancer/chemotherapeutic agents) and/or techniques (e.g., radiation therapies, surgical interventions, and the like) to a subject or in vitro cells, tissues, and organs. Preparation of gossypolone is included.

L14 ANSWER 3 OF 4 USPATFULL on STN
ACCESSION NUMBER: 2003:11220 USPATFULL
TITLE: Small molecule antagonists of Bcl-2 family proteins
INVENTOR(S): Wang, Shaomeng, Saline, MI, UNITED STATES
Yang, Dajun, Rockville, MD, UNITED STATES
PATENT ASSIGNEE(S): The Regents of the University of Michigan, Ann Arbor, MI (U.S. corporation)

	NUMBER	KIND	DATE

PATENT INFORMATION:	US 2003008924	A1	20030109
APPLICATION INFO.:	US 2002-158769	A1	20020530 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-293983P	20010530 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: MEDLEN & CARROLL, LLP, Suite 350, 101 Howard Street, San Francisco, CA, 94105
NUMBER OF CLAIMS: 92
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 19 Drawing Page(s)
LINE COUNT: 3132
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to naturally occurring and chemically synthesized small molecules antagonists of Bcl-2 family proteins. In particular, the present invention provides gossypol derivatives and methods of using gossypol derivatives as antagonists of the anti-apoptotic effects of Bcl-2 and Bcl-X.sub.L proteins especially in **cancer** cells that overexpress Bcl-2 family proteins (e.g., Bcl-2 and/or Bcl-X.sub.L).

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2002:927558 CAPLUS
DOCUMENT NUMBER: 138:19468
TITLE: Small molecule gossypol-related antagonists of Bcl-2 family proteins and inhibit the anti-apoptotic effects of Bcl-2 family proteins in **cancer** cells
INVENTOR(S): Wang, Shaomeng; Yang, Dajun
PATENT ASSIGNEE(S): The Regents of the University of Michigan, USA; Georgetown University Medical Center
SOURCE: PCT Int. Appl., 96 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002097053	A2	20021205	WO 2002-US17206	20020530
WO 2002097053	A3	20040910		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2449245	AA	20021205	CA 2002-2449245	20020530
NZ 529792	A	20031219	NZ 2002-529792	20020530
EP 1474121	A2	20041110	EP 2002-734614	20020530
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2005515158	T2	20050526	JP 2003-500222	20020530
US 2004214902	A1	20041028	US 2003-729156	20031205

PRIORITY APPLN. INFO.: US 2001-293983P P 20010530
US 2002-158769 A 20020530
WO 2002-US17206 W 20020530

AB The present invention relates to naturally occurring and chemical synthesized small mols. antagonists of Bcl-2 family proteins. In particular, the present invention provides gossypol derivs. and methods of using gossypol derivs. as antagonists of the anti-apoptotic effects of Bcl-2 and Bcl-XL proteins, especially in **cancer** cells that overexpress Bcl-2 family proteins (e.g., Bcl-2 and/or Bcl-XL). The invention uses a powerful structure-based virtual screening methodol. to identify small mol. antagonists of anti-apoptotic Bcl-2 family proteins, such as Bcl-2 and Bcl-XL, from large 3D chemical databases. The approach uses computational docking methods to identify potential small organic mol. inhibitors that bind to binding sites in the target proteins. In one embodiment, Bcl-XL protein was treated using the united atom approximation in the docking studies; only poly hydrogens were added to the protein, Kollman united-atom partial charges were assigned, and all water mols. were removed. Atomic solvation parameters and fragmental vols. were assigned tot he protein atoms using the AutoDock utility, AddSol. In another embodiment, the 3D structure of Bcl-2 was modeled using the MODELLER homol. modeling method. Using a 3-dimensional database containing approx. 7000 small organic compds. that were identified and isolated from Herbal medicines, 9 compds. with the highest DOCK score were obtained for further in vitro binding assays using an established sensitive and quant. in vitro fluorescence polarization-based binding assay. Bak peptide has an IC50 value of 0.3 μM for binding to BCL-XL, and binding is directly inhibited by gossypol. Thus, gossypol is a potent inhibitor for Bcl-XL, having a potency similar to that of the Bak peptide and it is also a moderately potent inhibitor for Bcl-2. Thus, a small mol. inhibitor (e.g., gossypol) blocks the anti-apoptotic functions of Bcl-2 and Bcl-XL which in turn induces apoptosis in **cancer** cells with elevated Bcl-2 and/or Bcl-XL expression. Gossypol inhibits cell **proliferation** (growth) in **cancer**, and more particularly, in a human breast **cancer** (MDA-MB-231 cell line) with an IC50 value of 2.0 μM.

=> log y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	29.34	87.28

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-1.46	-2.19

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NEWS  3  JUL 20  Powerful new interactive analysis and visualization software,
                 STN AnaVist, now available
NEWS  4  AUG 11  STN AnaVist workshops to be held in North America
NEWS  5  AUG 30  CA/CAplus -Increased access to 19th century research documents
NEWS  6  AUG 30  CASREACT - Enhanced with displayable reaction conditions
NEWS  7  SEP 09  ACD predicted properties enhanced in REGISTRY/ZREGISTRY
NEWS  8  OCT 03  MATHDI removed from STN
NEWS  9  OCT 04  CA/CAplus-Canadian Intellectual Property Office (CIPO) added
                 to core patent offices
NEWS 10  OCT 06  STN AnaVist workshops to be held in North America
NEWS 11  OCT 13  New CAS Information Use Policies Effective October 17, 2005
NEWS 12  OCT 17  STN(R) AnaVist(TM), Version 1.01, allows the export/download
                 of CAplus documents for use in third-party analysis and
                 visualization tools
NEWS 13  OCT 27  Free KWIC format extended in full-text databases
NEWS 14  OCT 27  DIOGENES content streamlined
NEWS 15  OCT 27  EPFULL enhanced with additional content

NEWS EXPRESS  JUNE 13 CURRENT WINDOWS VERSION IS V8.0, CURRENT
              MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
              AND CURRENT DISCOVER FILE IS DATED 13 JUNE 2005

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                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.21       0.21

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STRUCTURE FILE UPDATES:   27 OCT 2005  HIGHEST RN 866318-76-5
DICTIONARY FILE UPDATES:  27 OCT 2005  HIGHEST RN 866318-76-5

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=> s ethyl apogossypol
       7011832 ETHYL
            13 ETHYLS
       7011832 ETHYL
                  (ETHYL OR ETHYLS)
            10 APOGOSSYPOL
L1           2 ETHYL APOGOSSYPOL
                  (ETHYL(W)APOGOSSYPOL)

=> d tot

L1   ANSWER 1 OF 2  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   784206-49-1  REGISTRY
ED   Entered STN:  19 Nov 2004
CN   [2,2'-Binaphthalene]-1,1',6,6',7,7'-hexol, 5,5'-diethyl-3,3'-dimethyl-,
     (2S)- (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   (+)-Ethyl apogossypol
MF   C26 H26 O6
SR   CA
LC   STN Files:   CA, CAPLUS, TOXCENTER, USPATFULL
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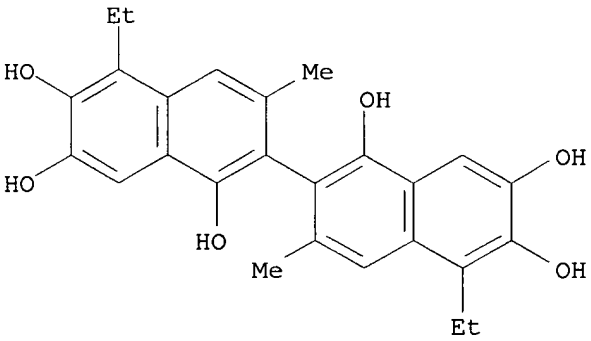
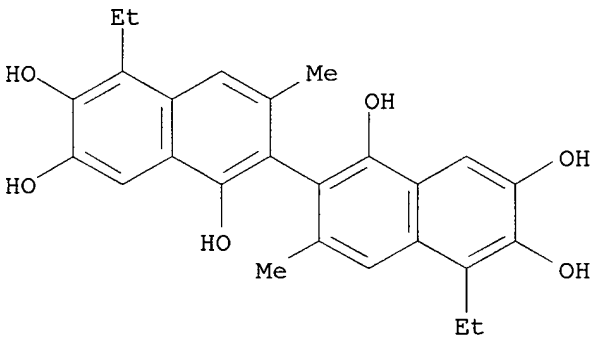


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2005 ACS on STN
RN 784206-47-9 REGISTRY
ED Entered STN: 19 Nov 2004
CN [2,2'-Binaphthalene]-1,1',6,6',7,7'-hexol, 5,5'-diethyl-3,3'-dimethyl-, (2R)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **(-)-Ethyl apogossypol**
MF C26 H26 O6
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> s ethyl apogossypol/cn
L2 0 ETHYL APOGOSSYPOL/CN

=> fil medl capl biosis uspatful wpids

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	18.34	18.55

FILE 'MEDLINE' ENTERED AT 14:18:14 ON 29 OCT 2005

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=> s l1
L3 3 L1

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=> dup rem
ENTER L# LIST OR (END):l3
PROCESSING COMPLETED FOR L3
L4            2 DUP REM L3 (1 DUPLICATE REMOVED)

=> d ibib abs tot

L4   ANSWER 1 OF 2  WPIDS  COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER:      2005-564053 [57]   WPIDS
CROSS REFERENCE:       2003-140460 [13]
DOC. NO. CPI:          C2005-170457
TITLE:                 Treating, ameliorating or preventing hyperproliferative
                       disease e.g., cancer in subject, involves administering
                       gossypol compound and anticancer agent to subject, or
                       administering gossypol compound and subjecting subject to
                       radiation.
DERWENT CLASS:         B04 B05
INVENTOR(S):           WANG, S; YANG, D
PATENT ASSIGNEE(S):    (GEOU) UNIV GEORGETOWN MEDICAL CENT; (UNMI) UNIV MICHIGAN
COUNTRY COUNT:         108
PATENT INFORMATION:

     PATENT NO        KIND DATE     WEEK      LA   PG
     ------------------------------------------------
     WO 2005069771    A2 20050804 (200557)* EN  262
        RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT
            KE LS LT LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG
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         W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE
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            KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ
            OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG
            US UZ VC VN YU ZA ZM ZW

APPLICATION DETAILS:

     PATENT NO       KIND                  APPLICATION          DATE
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     WO 2005069771   A2                   WO 2004-US40553      20041206


PRIORITY APPLN. INFO: US 2003-729156       20031205
AN   2005-564053 [57]   WPIDS
CR   2003-140460 [13]
AB   WO2005069771 A UPAB: 20050907
     NOVELTY - Treating, ameliorating or preventing (M1) a hyperproliferative
     disease in a subject, involves administering to the subject a gossypol
     compound and one or more second agent chosen from an anticancer agent and
     radiation, where the combination of ( plus or minus )-gossypol, heat, and
     radiation is not administered.
          DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the
     following:
          (1) a pharmaceutical composition (PC) comprising a gossypol compound
     and one or more anticancer agents; and
          (2) a kit comprising a gossypol compound, one or more anticancer
     agents, and instructions for administering the gossypol compound and the
     anticancer agents to a subject.
          ACTIVITY - Cytostatic; Anti-HIV; Vasotropic; Antiinflammatory;
     Antibacterial; Fungicide; Virucide.
          MECHANISM OF ACTION - Antagonist of Bcl-2 family proteins; Induces
     apoptosis; Inhibits cell proliferation. In vivo analysis of gossypol
     compounds in combination with radiation therapy in inhibiting cell
     proliferation was carried out in PC-3 xenograft mouse model as follows.
```

The xenograft mice (25) were divided into 5 groups. Group 1 (vehicle control) mice were orally administered with alcohol (10%), daily, Group 2 (radiation only) mice were subjected to radiation (2 Gy) 5 times/week for 2 weeks and orally administered daily with alcohol (10%), Group 3 (radiation plus gossypol) mice were subjected to radiation (2 Gy) 5 times/week for 3 weeks and orally administered daily with (-)-gossypol (10 mg/kg) every day for 4 weeks, Group 4 (gossypol only) mice were orally administered daily with (-)-gossypol (10 mg/kg) every day for 4 weeks, and Group 5 (control) mice were not subjected to treatment. During the treatment course, tumor sizes and animal weights were measured 3 times per/week for each animal. Treatment with (-)-gossypol alone or with radiation therapy alone had minimal antitumor effect. Results showed that there was more than 90% inhibition in tumor cell growth in animals receiving radiation therapy in combination with gossypol as compared to the group controls.

USE - (M1) is useful for treating, ameliorating or preventing a hyperproliferative disease in a subject, where the subject is a human. The disease is neoplastic disease. The hyperproliferative disease is cancer, preferably breast cancer, prostate cancer, pancreatic cancer, colon cancer, lung cancer, lymphoma, melanoma or head-neck cancer. The cancer is metastatic or is a tumor, where the treatment or amelioration results in regression of the tumor. The hyperproliferative disease is associated with overexpression of a Bcl-2 family member protein, where the Bcl-2 family protein is Bcl-2, Bcl-XL, Mcl-1, A1/BFL-1, BOO-DIVA, Bcl-w, Bcl-6, Bcl-8 or Bcl-y. The cancer is resistant to anticancer agent or radiation therapy (all claimed). PC is useful for treating hyperproliferative disease, tumor such as Wilm's tumor, metastatic cancer, cervical carcinoma, testicular carcinoma, genitourinary carcinoma, thyroid carcinoma, Hodgkin's disease, non-Hodgkin's sarcoma, etc. PC is useful for treating infections (e.g., bacterial, viral, fungal and mycoplasma infections), AIDS, inflammatory disease, vascular diseases, etc. PC is useful for preventing the onset or spread of neoplastic disease, for treating diseased cells, tissues, organs or pathological conditions and/or disease states in a subject, and for modulating cell division in a tissue.

ADVANTAGE - PC is less toxic and more tolerable.

DESCRIPTION OF DRAWING(S) - The figure is a graph representing the tumor size in PC-3 xenograft model mice subjected to radiation and/or gossypol treatments.

Dwg.36/46

L4 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 1

ACCESSION NUMBER: 2004:907153 CAPLUS
DOCUMENT NUMBER: 141:388644
TITLE: Gossypol compound antagonists of Bcl-2 family proteins, and use with with other therapeutic means in the treatment of neoplastic and other diseases
INVENTOR(S): Wang, Shaomeng; Yang, Dajun
PATENT ASSIGNEE(S): The Regents of the University of Michigan, USA; Georgetown University
SOURCE: U.S. Pat. Appl. Publ., 143 pp., Cont.-in-part of U.S. Ser. No. 158,769.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004214902	A1	20041028	US 2003-729156	20031205
WO 2002097053	A2	20021205	WO 2002-US17206	20020530
WO 2002097053	A3	20040910		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,

CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
UA, UG, US, UZ, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB,
GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA,
GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2003008924 A1 20030109 US 2002-158769 20020530
WO 2005069771 A2 20050804 WO 2004-US40553 20041206
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
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EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT,
RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-293983P P 20010530
US 2002-158769 A2 20020530
WO 2002-US17206 A2 20020530
US 2003-729156 A 20031205

AB The invention relates to naturally occurring and chemical synthesized small mol. antagonists of Bcl-2 family proteins. In particular, the invention provides gossypol compds. (e.g., isomers, enantiomers, racemic compds., metabolites, derivs., pharmaceutically acceptable salts, in combination with acids or bases, and the like) and methods of using these compds. as antagonists of the anti-apoptotic effects of Bcl-2 family member proteins (e.g., Bcl-2, Bcl-XL, and the like). The invention also provides compns. comprising gossypol compds. and optionally one or more addnl. therapeutic agents (e.g., anticancer/chemotherapeutic agents). The invention also provides methods for treating diseases and pathologies (e.g., neoplastic diseases) comprising administering a composition comprising gossypol compds. and optionally one or more addnl. therapeutic agents (e.g., anticancer/chemotherapeutic agents) and/or techniques (e.g., radiation therapies, surgical interventions, and the like) to a subject or in vitro cells, tissues, and organs. Preparation of gossypolone is included.

=> fil reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	13.55	32.10

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-0.73	-0.73

FILE 'REGISTRY' ENTERED AT 14:18:44 ON 29 OCT 2005

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 27 OCT 2005 HIGHEST RN 866318-76-5
DICTIONARY FILE UPDATES: 27 OCT 2005 HIGHEST RN 866318-76-5

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

Please note that search-term pricing does apply when conducting SmartSELECT searches.

****
* *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
* *
****

Structure search iteration limits have been increased. See HELP SLIMITS for details.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

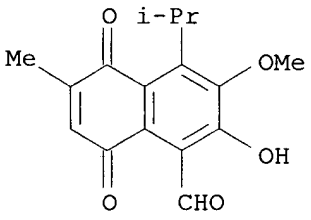
http://www.cas.org/ONLINE/UG/regprops.html

=> s hemigossypolone/cn
L5 1 HEMIGOSSYPOLONE/CN

=> s hemigossypolone
L6 4 HEMIGOSSYPOLONE

=> d scan

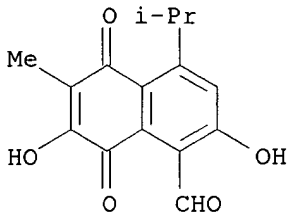
L6 4 ANSWERS REGISTRY COPYRIGHT 2005 ACS on STN
IN 1-Naphthalenecarboxaldehyde, 5,8-dihydro-2-hydroxy-3-methoxy-6-methyl-4-(1-methylethyl)-5,8-dioxo- (9CI)
MF C16 H16 O5



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):3

L6 4 ANSWERS REGISTRY COPYRIGHT 2005 ACS on STN
IN 1-Naphthalenecarboxaldehyde, 5,8-dihydro-2,7-dihydroxy-6-methyl-4-(1-methylethyl)-5,8-dioxo- (9CI)
MF C15 H14 O5



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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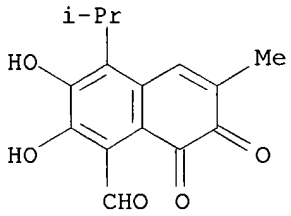

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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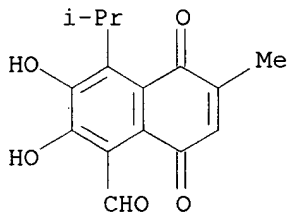
IN 1-Naphthalenecarboxaldehyde, 5,8-dihydro-2,3-dihydroxy-6-methyl-4-(1-methylethyl)-5,8-dioxo- (9CI)
MF C15 H14 O5
CI COM



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

ALL ANSWERS HAVE BEEN SCANNED

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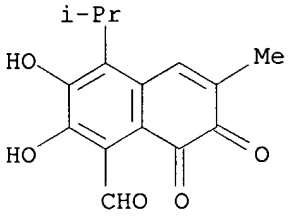
L6 ANSWER 1 OF 4 REGISTRY COPYRIGHT 2005 ACS on STN
RN 76628-01-8 REGISTRY
ED Entered STN: 16 Nov 1984
CN 1-Naphthalenecarboxaldehyde, 7,8-dihydro-2,3-dihydroxy-6-methyl-4-(1-methylethyl)-7,8-dioxo- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **o-Hemigossypolone**
FS 3D CONCORD
MF C15 H14 O5
LC STN Files: CA, CAPLUS, SPECINFO



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L6 ANSWER 2 OF 4 REGISTRY COPYRIGHT 2005 ACS on STN
RN 69688-68-2 REGISTRY
ED Entered STN: 16 Nov 1984
CN 1-Naphthalenecarboxaldehyde, 5,8-dihydro-2,7-dihydroxy-6-methyl-4-(1-methylethyl)-5,8-dioxo- (9CI) (CA INDEX NAME)
OTHER NAMES:
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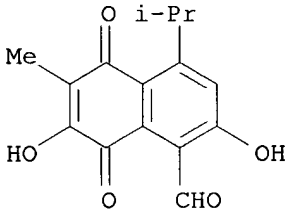
LC STN Files: AGRICOLA, BIOSIS, CA, CAPLUS, TOXCENTER

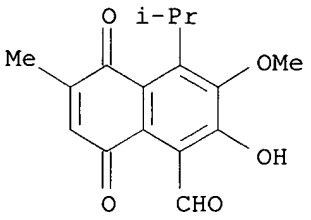


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L6 ANSWER 3 OF 4 REGISTRY COPYRIGHT 2005 ACS on STN
RN 35839-49-7 REGISTRY
ED Entered STN: 16 Nov 1984
CN 1-Naphthalenecarboxaldehyde, 5,8-dihydro-2-hydroxy-3-methoxy-6-methyl-4-(1-methylethyl)-5,8-dioxo- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **Hemigossypolone 7-methyl ether**
MF C16 H16 O5

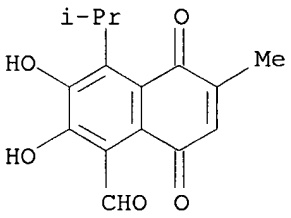
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, SPECINFO
(*File contains numerically searchable property data)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

6 REFERENCES IN FILE CA (1907 TO DATE)
6 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L6 ANSWER 4 OF 4 REGISTRY COPYRIGHT 2005 ACS on STN
RN 35688-47-2 REGISTRY
ED Entered STN: 16 Nov 1984
CN 1-Naphthalenecarboxaldehyde, 5,8-dihydro-2,3-dihydroxy-6-methyl-4-(1-methylethyl)-5,8-dioxo- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **Hemigossypolone**
CN NSC 650936
CN **p-Hemigossypolone**
MF C15 H14 O5
CI COM
LC STN Files: AGRICOLA, BEILSTEIN*, BIOSIS, CA, CAPLUS, NAPRALERT, SPECINFO, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

38 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
38 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> sel rn name 1,2,4
E1 THROUGH E8 ASSIGNED

=> FIL MEDL CAPL BIOSIS USPATFUL WPIDS

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	18.59	50.69

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE	TOTAL

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                                                          ENTRY    SESSION
CA SUBSCRIBER PRICE                                        0.00      -0.73

FILE 'MEDLINE' ENTERED AT 14:19:51 ON 29 OCT 2005

FILE 'CAPLUS' ENTERED AT 14:19:51 ON 29 OCT 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'BIOSIS' ENTERED AT 14:19:51 ON 29 OCT 2005
Copyright (c) 2005 The Thomson Corporation

FILE 'USPATFULL' ENTERED AT 14:19:51 ON 29 OCT 2005
CA INDEXING COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'WPIDS' ENTERED AT 14:19:51 ON 29 OCT 2005
COPYRIGHT (C) 2005 THE THOMSON CORPORATION

=> s e1-8
L7          80 (HEMIGOSSYPOLONE/BI OR ISOHEMIGOSSYPOLONE/BI OR "NSC 650936"/BI
               OR O-HEMIGOSSYPOLONE/BI OR P-HEMIGOSSYPOLONE/BI OR 35688-47-2/BI
                OR 69688-68-2/BI OR 76628-01-8/BI)

=> s cancer or carcinoma or proliferat?
L8     2737782 CANCER OR CARCINOMA OR PROLIFERAT?

=> s l7 and l8
L9           6 L7 AND L8

=> dup rem l9
PROCESSING COMPLETED FOR L9
L10          4 DUP REM L9 (2 DUPLICATES REMOVED)

=> d ibib abs tot

L10  ANSWER 1 OF 4  WPIDS  COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER:     2005-564053 [57]   WPIDS
CROSS REFERENCE:      2003-140460 [13]
DOC. NO. CPI:         C2005-170457
TITLE:                Treating, ameliorating or preventing hyperproliferative
                      disease e.g., cancer in subject, involves
                      administering gossypol compound and anticancer agent to
                      subject, or administering gossypol compound and
                      subjecting subject to radiation.
DERWENT CLASS:        B04 B05
INVENTOR(S):          WANG, S; YANG, D
PATENT ASSIGNEE(S):   (GEOU) UNIV GEORGETOWN MEDICAL CENT; (UNMI) UNIV MICHIGAN
COUNTRY COUNT:        108
PATENT INFORMATION:

     PATENT NO       KIND DATE     WEEK      LA   PG
     ---------------------------------------------
     WO 2005069771   A2 20050804 (200557)* EN  262
        RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT
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            OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG
            US UZ VC VN YU ZA ZM ZW
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APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2005069771	A2	WO 2004-US40553	20041206

PRIORITY APPLN. INFO: US 2003-729156 20031205
AN 2005-564053 [57] WPIDS
CR 2003-140460 [13]
AB WO2005069771 A UPAB: 20050907
NOVELTY - Treating, ameliorating or preventing (M1) a hyperproliferative disease in a subject, involves administering to the subject a gossypol compound and one or more second agent chosen from an anticancer agent and radiation, where the combination of (plus or minus)-gossypol, heat, and radiation is not administered.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a pharmaceutical composition (PC) comprising a gossypol compound and one or more anticancer agents; and

(2) a kit comprising a gossypol compound, one or more anticancer agents, and instructions for administering the gossypol compound and the anticancer agents to a subject.

ACTIVITY - Cytostatic; Anti-HIV; Vasotropic; Antiinflammatory; Antibacterial; Fungicide; Virucide.

MECHANISM OF ACTION - Antagonist of Bcl-2 family proteins; Induces apoptosis; Inhibits cell **proliferation**. In vivo analysis of gossypol compounds in combination with radiation therapy in inhibiting cell **proliferation** was carried out in PC-3 xenograft mouse model as follows. The xenograft mice (25) were divided into 5 groups. Group 1 (vehicle control) mice were orally administered with alcohol (10%), daily, Group 2 (radiation only) mice were subjected to radiation (2 Gy) 5 times/week for 2 weeks and orally administered daily with alcohol (10%), Group 3 (radiation plus gossypol) mice were subjected to radiation (2 Gy) 5 times/week for 3 weeks and orally administered daily with (-)-gossypol (10 mg/kg) every day for 4 weeks, Group 4 (gossypol only) mice were orally administered daily with (-)-gossypol (10 mg/kg) every day for 4 weeks, and Group 5 (control) mice were not subjected to treatment. During the treatment course, tumor sizes and animal weights were measured 3 times per/week for each animal. Treatment with (-)-gossypol alone or with radiation therapy alone had minimal antitumor effect. Results showed that there was more than 90% inhibition in tumor cell growth in animals receiving radiation therapy in combination with gossypol as compared to the group controls.

USE - (M1) is useful for treating, ameliorating or preventing a hyperproliferative disease in a subject, where the subject is a human. The disease is neoplastic disease. The hyperproliferative disease is **cancer**, preferably breast **cancer**, prostate **cancer**, pancreatic **cancer**, colon **cancer**, lung **cancer**, lymphoma, melanoma or head-neck **cancer**. The **cancer** is metastatic or is a tumor, where the treatment or amelioration results in regression of the tumor. The hyperproliferative disease is associated with overexpression of a Bcl-2 family member protein, where the Bcl-2 family protein is Bcl-2, Bcl-XL, Mcl-1, A1/BFL-1, BOO-DIVA, Bcl-w, Bcl-6, Bcl-8 or Bcl-y. The **cancer** is resistant to anticancer agent or radiation therapy (all claimed). PC is useful for treating hyperproliferative disease, tumor such as Wilm's tumor, metastatic **cancer**, cervical **carcinoma**, testicular **carcinoma**, genitourinary **carcinoma**, thyroid **carcinoma**, Hodgkin's disease, non-Hodgkin's sarcoma, etc. PC is useful for treating infections (e.g., bacterial, viral, fungal and mycoplasma infections), AIDS, inflammatory disease, vascular diseases, etc. PC is useful for preventing the onset or spread of neoplastic

disease, for treating diseased cells, tissues, organs or pathological conditions and/or disease states in a subject, and for modulating cell division in a tissue.

ADVANTAGE - PC is less toxic and more tolerable.

DESCRIPTION OF DRAWING(S) - The figure is a graph representing the tumor size in PC-3 xenograft model mice subjected to radiation and/or gossypol treatments.

Dwg.36/46

L10 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 1

ACCESSION NUMBER: 2004:907153 CAPLUS
DOCUMENT NUMBER: 141:388644
TITLE: Gossypol compound antagonists of Bcl-2 family proteins, and use with with other therapeutic means in the treatment of neoplastic and other diseases
INVENTOR(S): Wang, Shaomeng; Yang, Dajun
PATENT ASSIGNEE(S): The Regents of the University of Michigan, USA; Georgetown University
SOURCE: U.S. Pat. Appl. Publ., 143 pp., Cont.-in-part of U.S. Ser. No. 158,769.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004214902	A1	20041028	US 2003-729156	20031205
WO 2002097053	A2	20021205	WO 2002-US17206	20020530
WO 2002097053	A3	20040910		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2003008924	A1	20030109	US 2002-158769	20020530
WO 2005069771	A2	20050804	WO 2004-US40553	20041206

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RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:	US 2001-293983P	P	20010530
	US 2002-158769	A2	20020530
	WO 2002-US17206	A2	20020530
	US 2003-729156	A	20031205

AB The invention relates to naturally occurring and chemical synthesized small mol. antagonists of Bcl-2 family proteins. In particular, the invention provides gossypol compds. (e.g., isomers, enantiomers, racemic compds., metabolites, derivs., pharmaceutically acceptable salts, in combination with acids or bases, and the like) and methods of using these compds. as

antagonists of the anti-apoptotic effects of Bcl-2 family member proteins (e.g., Bcl-2, Bcl-XL, and the like). The invention also provides compns. comprising gossypol compds. and optionally one or more addnl. therapeutic agents (e.g., anticancer/chemotherapeutic agents). The invention also provides methods for treating diseases and pathologies (e.g., neoplastic diseases) comprising administering a composition comprising gossypol compds. and optionally one or more addnl. therapeutic agents (e.g., anticancer/chemotherapeutic agents) and/or techniques (e.g., radiation therapies, surgical interventions, and the like) to a subject or in vitro cells, tissues, and organs. Preparation of gossypolone is included.

L10 ANSWER 3 OF 4 USPATFULL on STN

ACCESSION NUMBER:	2003:11220 USPATFULL			
TITLE:	Small molecule antagonists of Bcl-2 family proteins			
INVENTOR(S):	Wang, Shaomeng, Saline, MI, UNITED STATES Yang, Dajun, Rockville, MD, UNITED STATES			
PATENT ASSIGNEE(S):	The Regents of the University of Michigan, Ann Arbor, MI (U.S. corporation)			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003008924	A1	20030109	
APPLICATION INFO.:	US 2002-158769	A1	20020530	(10)
	NUMBER		DATE	
PRIORITY INFORMATION:	US 2001-293983P		20010530	(60)
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	APPLICATION			
LEGAL REPRESENTATIVE:	MEDLEN & CARROLL, LLP, Suite 350, 101 Howard Street, San Francisco, CA, 94105			
NUMBER OF CLAIMS:	92			
EXEMPLARY CLAIM:	1			
NUMBER OF DRAWINGS:	19 Drawing Page(s)			
LINE COUNT:	3132			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to naturally occurring and chemically synthesized small molecules antagonists of Bcl-2 family proteins. In particular, the present invention provides gossypol derivatives and methods of using gossypol derivatives as antagonists of the anti-apoptotic effects of Bcl-2 and Bcl-X.sub.L proteins especially in **cancer** cells that overexpress Bcl-2 family proteins (e.g., Bcl-2 and/or Bcl-X.sub.L).

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 2

ACCESSION NUMBER:	2002:927558 CAPLUS
DOCUMENT NUMBER:	138:19468
TITLE:	Small molecule gossypol-related antagonists of Bcl-2 family proteins and inhibit the anti-apoptotic effects of Bcl-2 family proteins in **cancer** cells
INVENTOR(S):	Wang, Shaomeng; Yang, Dajun
PATENT ASSIGNEE(S):	The Regents of the University of Michigan, USA; Georgetown University Medical Center
SOURCE:	PCT Int. Appl., 96 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2002097053	A2	20021205	WO 2002-US17206	20020530
WO 2002097053	A3	20040910		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2449245	AA	20021205	CA 2002-2449245	20020530
NZ 529792	A	20031219	NZ 2002-529792	20020530
EP 1474121	A2	20041110	EP 2002-734614	20020530

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

JP 2005515158	T2	20050526	JP 2003-500222	20020530
US 2004214902	A1	20041028	US 2003-729156	20031205

PRIORITY APPLN. INFO.:	US 2001-293983P	P	20010530
	US 2002-158769	A	20020530
	WO 2002-US17206	W	20020530

AB The present invention relates to naturally occurring and chemical synthesized small mols. antagonists of Bcl-2 family proteins. In particular, the present invention provides gossypol derivs. and methods of using gossypol derivs. as antagonists of the anti-apoptotic effects of Bcl-2 and Bcl-XL proteins, especially in **cancer** cells that overexpress Bcl-2 family proteins (e.g., Bcl-2 and/or Bcl-XL). The invention uses a powerful structure-based virtual screening methodol. to identify small mol. antagonists of anti-apoptotic Bcl-2 family proteins, such as Bcl-2 and Bcl-XL, from large 3D chemical databases. The approach uses computational docking methods to identify potential small organic mol. inhibitors that bind to binding sites in the target proteins. In one embodiment, Bcl-XL protein was treated using the united atom approximation in the docking studies; only poly hydrogens were added to the protein, Kollman united-atom partial charges were assigned, and all water mols. were removed. Atomic solvation parameters and fragmental vols. were assigned tot he protein atoms using the AutoDock utility, AddSol. In another embodiment, the 3D structure of Bcl-2 was modeled using the MODELLER homol. modeling method. Using a 3-dimensional database containing approx. 7000 small organic compds. that were identified and isolated from Herbal medicines, 9 compds. with the highest DOCK score were obtained for further in vitro binding assays using an established sensitive and quant. in vitro fluorescence polarization-based binding assay. Bak peptide has an IC50 value of 0.3 μM for binding to BCL-XL, and binding is directly inhibited by gossypol. Thus, gossypol is a potent inhibitor for Bcl-XL, having a potency similar to that of the Bak peptide and it is also a moderately potent inhibitor for Bcl-2. Thus, a small mol. inhibitor (e.g., gossypol) blocks the anti-apoptotic functions of Bcl-2 and Bcl-XL which in turn induces apoptosis in **cancer** cells with elevated Bcl-2 and/or Bcl-XL expression. Gossypol inhibits cell **proliferation** (growth) in **cancer**, and more particularly, in a human breast **cancer** (MDA-MB-231 cell line) with an IC50 value of 2.0 μM.

```
=> s apoptosis
L11     353484 APOPTOSIS

=> s l7 and l11
L12          6 L7 AND L11

=> s l12 not l10
```

L13 2 L12 NOT L10

=> d ibib abs tot

L13 ANSWER 1 OF 2 USPATFULL on STN

ACCESSION NUMBER:	2004:274400 USPATFULL
TITLE:	Small molecule antagonists of BCL-2 family proteins
INVENTOR(S):	Wang, Shaomeng, Saline, MI, UNITED STATES Yang, Dajun, Rockville, MD, UNITED STATES
PATENT ASSIGNEE(S):	The Regents of the University of Michigan, Ann Arbor, MI (U.S. corporation) Georgetown University, Washington, DC (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004214902	A1	20041028
APPLICATION INFO.:	US 2003-729156	A1	20031205 (10)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2002-158769, filed on 30 May 2002, ABANDONED Continuation-in-part of Ser. No. WO 2002-US17206, filed on 30 May 2002, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-293983P	20010530 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	David A. Casimir, MEDLEN & CARROLL, LLP, Suite 350, 101 Howard Street, San Francisco, CA, 94105
NUMBER OF CLAIMS:	51
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	55 Drawing Page(s)
LINE COUNT:	8211

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to naturally occurring and chemically synthesized small molecule antagonists of Bcl-2 family proteins. In particular, the present invention provides gossypol compounds (e.g., isomers, enantiomers, racemic compounds, metabolites, derivatives, pharmaceutically acceptable salts, in combination with acids or bases, and the like) and methods of using these compounds as antagonists of the anti-apoptotic effects of Bcl-2 family member proteins (e.g., Bcl-2, Bcl-X.sub.L, and the like). The present invention also provides compositions comprising gossypol compounds and optionally one or more additional therapeutic agents (e.g., anticancer/chemotherapeutic agents). The present invention also provides methods for treating diseases and pathologies (e.g., neoplastic diseases) comprising administering a composition comprising gossypol compounds and optionally one or more additional therapeutic agents (e.g., anticancer/chemotherapeutic agents) and/or techniques (e.g., radiation therapies, surgical interventions, and the like) to a subject or in vitro cells, tissues, and organs.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L13 ANSWER 2 OF 2 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER:	2003-140460 [13] WPIDS
CROSS REFERENCE:	2005-564053 [57]
DOC. NO. CPI:	C2003-035675
TITLE:	Modulating **apoptosis** or cell division in a tissue, treating a subject overexpressing Bcl-2 family protein, and treating cancer in a subject, by administering gossypol compound to the cell, tissue or subject.

DERWENT CLASS: B04 D16
INVENTOR(S): WANG, S; YANG, D
PATENT ASSIGNEE(S): (UNMI) UNIV MICHIGAN; (GEOU) UNIV GEORGETOWN MEDICAL CENT; (GEOU) UNIV GEORGETOWN
COUNTRY COUNT: 101
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002097053	A2	20021205	(200313)*	EN	96
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW					
US 2003008924	A1	20030109	(200313)		
NO 2003005301	A	20040130	(200419)		
AU 2002305769	A1	20021209	(200452)		
US 2004214902	A1	20041028	(200471)		
EP 1474121	A2	20041110	(200473)	EN	
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KR 2004108528	A	20041224	(200528)		
JP 2005515158	W	20050526	(200535)		55
CN 1589135	A	20050302	(200537)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002097053	A2	WO 2002-US17206	20020530
US 2003008924	A1 Provisional	US 2001-293983P	20010530
		US 2002-158769	20020530
NO 2003005301	A	WO 2002-US17206	20020530
		NO 2003-5301	20031128
AU 2002305769	A1	AU 2002-305769	20020530
US 2004214902	A1 Provisional	US 2001-293983P	20010530
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		US 2003-729156	20031205
EP 1474121	A2	EP 2002-734614	20020530
		WO 2002-US17206	20020530
KR 2004108528	A	KR 2003-715683	20031129
JP 2005515158	W	WO 2002-US17206	20020530
		JP 2003-500222	20020530
CN 1589135	A	CN 2002-813299	20020530

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2002305769	A1 Based on	WO 2002097053
EP 1474121	A2 Based on	WO 2002097053
JP 2005515158	W Based on	WO 2002097053

PRIORITY APPLN. INFO: US 2002-158769 20020530; US 2001-293983P 20010530; US 2003-729156 20031205
AN 2003-140460 [13] WPIDS
CR 2005-564053 [57]
AB WO 200297053 A UPAB: 20050907

NOVELTY - Modulating (M1) **apoptosis** in a cell, modulating cell division in a tissue, treating a subject overexpressing Bcl-2 family protein, and treating cancer in a subject, comprising administering gossypol compound (I) to the cell, tissue or subject, is new.

DETAILED DESCRIPTION - Modulating (M1) **apoptosis** in a cell, modulating cell division in a tissue, treating a subject overexpressing Bcl-2 family protein, and treating cancer in a subject, comprising:

(a) modulating **apoptosis**, by treating a cell that overexpresses Bcl-2 family protein, with an effective amount of (I);

(b) modulating cell division in a tissue, by treating a tissue that overexpresses Bcl-2 family protein, with effective amounts of (I) and an anticancer agent;

(c) treating a subject overexpressing a Bcl-2 family protein, by administering (I) and optionally an anticancer agent, to the subject; and

(d) treating cancer in a subject, by administering an effective amount (I) and optionally an anticancer agent, to a patient having a condition characterized by overexpression of Bcl-2 family protein, to a patient having cancer characterized by overexpression of Bcl-2 family protein, or to a patient characterized by resistance to cancer therapies, where the dose of (I) and anticancer agent is sufficient to reduce the overexpression of the Bcl-2 protein.

INDEPENDENT CLAIMS are also included for the following:

(1) a pharmaceutical composition (PC) comprising (I) and instructions for administering (I) to a subject characterized by overexpression of a Bcl-2 family protein or by resistance to a cancer therapy; and

(2) screening (M2) a gossypol compound and a test compound, by contacting a first group of cells with (I) and a test compound, and observing the effects of contacting the first group of cells with (I) and the test compound.

ACTIVITY - Cytostatic; Anti-HIV; Antibacterial; Virucide; Fungicide.

MECHANISM OF ACTION - Antagonists Bcl-2 family proteins; Modulator of **apoptosis** and cell division; Inhibitor of tumor growth.

The MDA-MB-231 breast cancer cell line has a high level of both Bcl-2 and Bcl-XL expression. The ability of gossypol to inhibit MDA-MB-231 cell growth was tested in a 5 day 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay. Gossypol was shown to inhibit MDA-MB-231 cell growth with an IC50 value of 2.0 micro M. Treatment of MDA-MB-231 cancer cells with gossypol induced **apoptosis** in the cancer cells, but not in normal WI-38 fibroblast cells. In other tests, gossypol was shown to induce **apoptosis** in T-47D breast cancer cells that have high levels of Bcl-XL expression, but low levels of Bcl-2 expression. It was also found that gossypol induces **apoptosis** in other cancer cell lines with high Bcl-XL such as, human colon cancer cell line HT-29, but not in cancer cell lines with low Bcl-2 and low Bcl-XL expression, such as prostate cancer cell line DU-145.

USE - M1 or PC is useful for modulating **apoptosis** in a diseased cell (e.g. hyperproliferative disease, cancer, AIDS, degenerative condition, vascular disease and infection by pathogen e.g. bacteria, fungi or virus), modulating cell division in a tissue, treating a subject having a condition characterized by overexpression of Bcl-2 family protein, and treating cancer in a subject, where the cancer includes cancer of breast, prostate, skin, pancreas, colon, ovary, brain, liver, bladder, non-small lung or cervix, or melanoma, carcinoma, myeloma, adrenal carcinoma, lymphoma, leukemia, neuroblastoma, glioblastoma and head-neck cancer. The cancer may be metastatic or resistant to cancer therapy including chemotherapy, radiation therapy or hormone treatment. (All claimed.)

Dwg.0/17

=> log h

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	51.97	102.66

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DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)       SINCE FILE      TOTAL
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CA SUBSCRIBER PRICE                                   -1.46      -2.19

 SESSION WILL BE HELD FOR 60 MINUTES
STN INTERNATIONAL SESSION SUSPENDED AT 14:22:09 ON 29 OCT 2005

Connecting via Winsock to STN



Welcome to STN International!  Enter x:x

LOGINID:ssspta1617srh

PASSWORD:
 * * * * * * RECONNECTED TO STN INTERNATIONAL * * * * * *
SESSION RESUMED IN FILE 'MEDLINE, CAPLUS, BIOSIS, USPATFULL, WPIDS'
AT 14:32:21 ON 29 OCT 2005
FILE 'MEDLINE' ENTERED AT 14:32:21 ON 29 OCT 2005
FILE 'CAPLUS' ENTERED AT 14:32:21 ON 29 OCT 2005
COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY (ACS)
FILE 'BIOSIS' ENTERED AT 14:32:21 ON 29 OCT 2005
Copyright (c) 2005 The Thomson Corporation
FILE 'USPATFULL' ENTERED AT 14:32:21 ON 29 OCT 2005
CA INDEXING COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY (ACS)
FILE 'WPIDS' ENTERED AT 14:32:21 ON 29 OCT 2005
COPYRIGHT (C) 2005 THE THOMSON CORPORATION

COST IN U.S. DOLLARS                             SINCE FILE      TOTAL
                                                      ENTRY    SESSION
FULL ESTIMATED COST                                   51.97     102.66

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)       SINCE FILE      TOTAL
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L2             0 S ETHYL APOGOSSYPOL/CN

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L3             3 S L1
L4             2 DUP REM L3 (1 DUPLICATE REMOVED)

     FILE 'REGISTRY' ENTERED AT 14:18:44 ON 29 OCT 2005
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L6             4 S HEMIGOSSYPOLONE
                 SEL RN NAME 1,2,4

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L7            80 S E1-8
L8       2737782 S CANCER OR CARCINOMA OR PROLIFERAT?
L9             6 S L7 AND L8
L10            4 DUP REM L9 (2 DUPLICATES REMOVED)
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L12           6 S L7 AND L11
L13           2 S L12 NOT L10

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DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
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CA SUBSCRIBER PRICE                                    -1.46      -2.19

FILE 'REGISTRY' ENTERED AT 14:32:37 ON 29 OCT 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2005 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   27 OCT 2005  HIGHEST RN 866318-76-5
DICTIONARY FILE UPDATES:  27 OCT 2005  HIGHEST RN 866318-76-5

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

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*                                                                    *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,   *
* effective March 20, 2005.  A new display format, IDERL, is now    *
* available and contains the CA role and document type information. *
*                                                                    *
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Structure search iteration limits have been increased.  See HELP SLIMITS
for details.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=> s apogossypol
L14          10 APOGOSSYPOL

=> d scan

L14  10 ANSWERS   REGISTRY  COPYRIGHT 2005 ACS on STN
IN   Apogossypolic acid, dimethyl ester (4CI)
MF   C15 H20 O6
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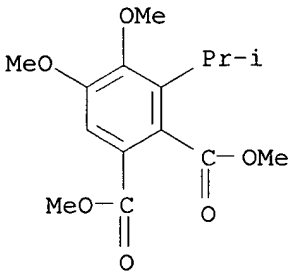

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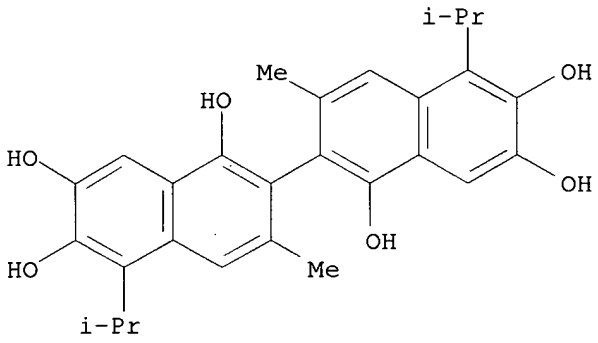

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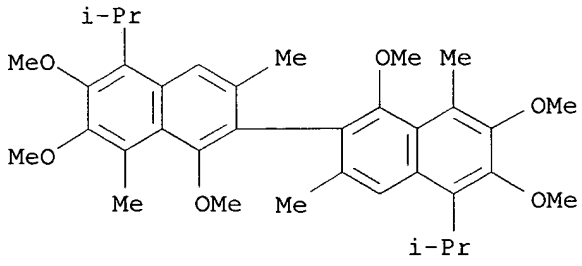

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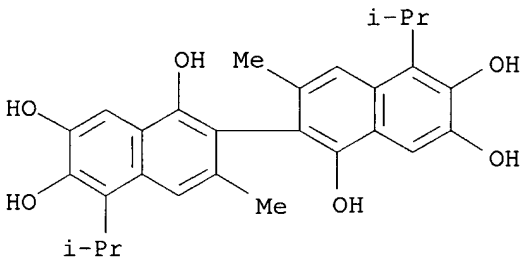

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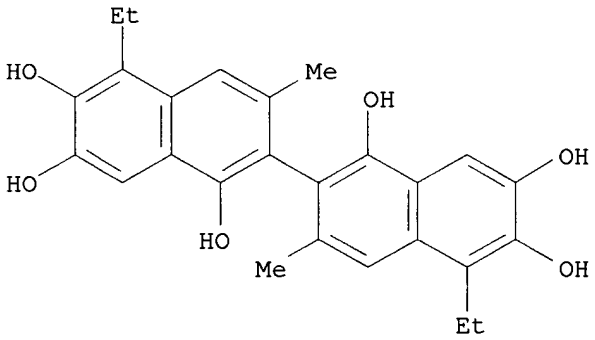

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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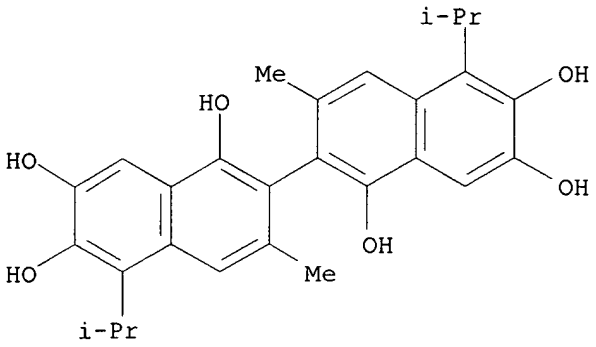

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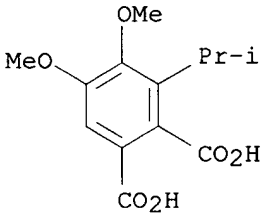

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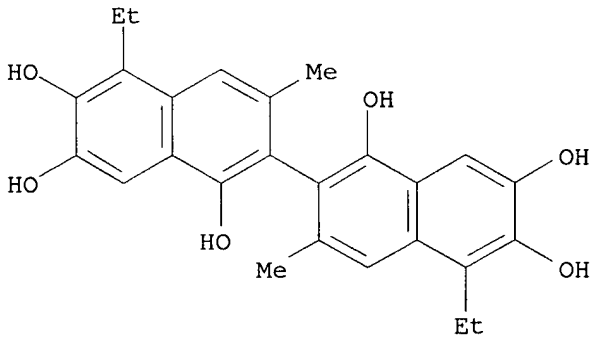

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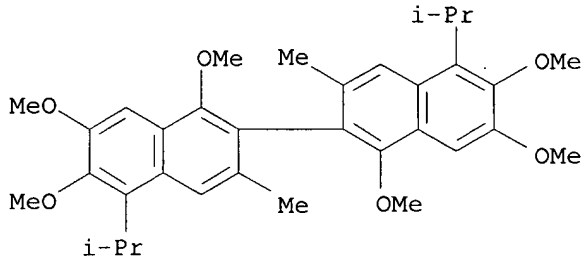

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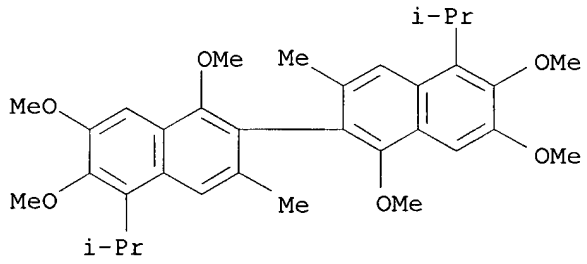

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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L15          2 L14 AND C34 H42 O6/MF

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ED   Entered STN:  02 Apr 1996
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     methylethyl)-, (1S)- (9CI)  (CA INDEX NAME)
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OTHER CA INDEX NAMES:
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OTHER NAMES:
CN **(+)-Apogossypol hexamethyl ether**
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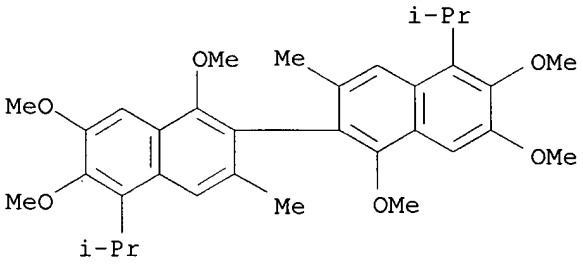
SR CA
LC STN Files: BIOSIS, CA, CAPLUS, CASREACT



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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RN 7144-61-8 REGISTRY
ED Entered STN: 16 Nov 1984
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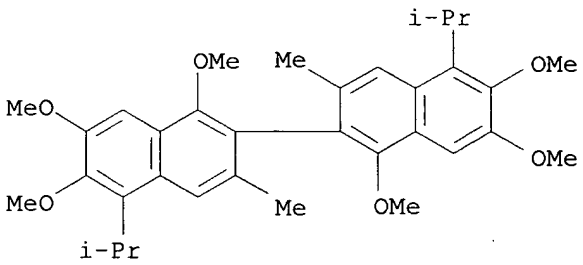
OTHER CA INDEX NAMES:
CN 2,2'-Binaphthyl, 5,5'-diisopropyl-1,1',6,6',7,7'-hexamethoxy-3,3'-dimethyl- (6CI, 8CI)
OTHER NAMES:
CN **(±)-Apogossypol hexamethyl ether**
CN NSC 40279
CN SK 31348
FS 3D CONCORD
DR 40323-50-0
MF **C34 H42 O6**
LC STN Files: BEILSTEIN*, CA, CAOLD, CAPLUS, CASREACT, CHEMCATS
(*File contains numerically searchable property data)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

13 REFERENCES IN FILE CA (1907 TO DATE)
13 REFERENCES IN FILE CAPLUS (1907 TO DATE)

3 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

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L16 1 APOGOSSYPOL/CN

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L16 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2005 ACS on STN
RN 66389-74-0 REGISTRY
ED Entered STN: 16 Nov 1984
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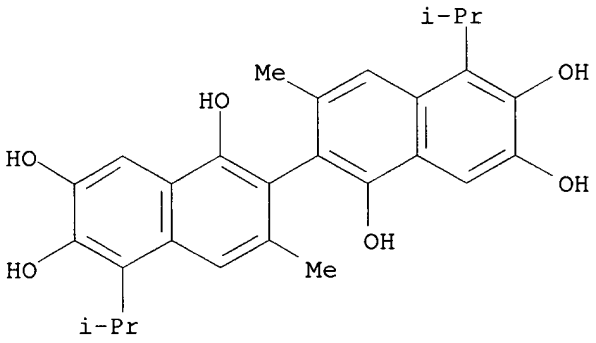
OTHER NAMES:
CN **Apogossypol**
MF C28 H30 O6
LC STN Files: BEILSTEIN*, BIOSIS, CA, CAPLUS, CASREACT, DDFU, DRUGU, NAPRALERT, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)



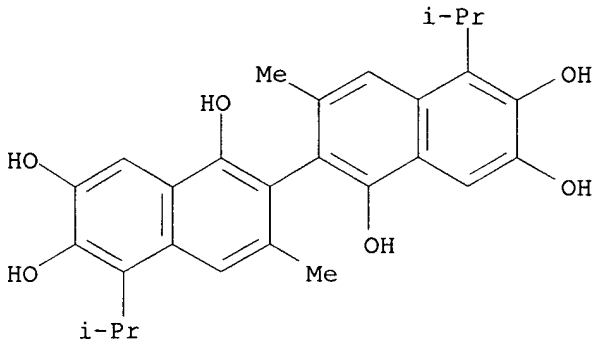
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

19 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
19 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> s l14 and C28 H30 O6/mf
476 C28 H30 O6/MF
L17 3 L14 AND C28 H30 O6/MF

=> d tot

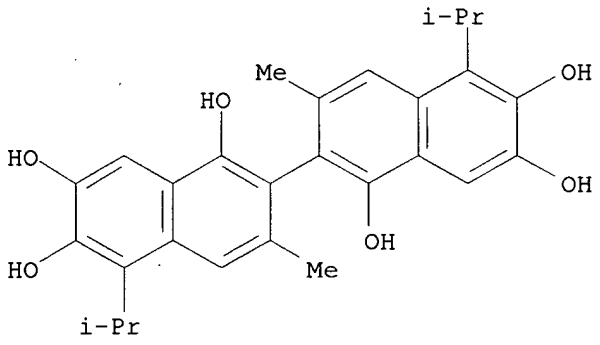
L17 ANSWER 1 OF 3 REGISTRY COPYRIGHT 2005 ACS on STN
RN 784206-41-3 REGISTRY
ED Entered STN: 19 Nov 2004
CN [2,2'-Binaphthalene]-1,1',6,6',7,7'-hexol, 3,3'-dimethyl-5,5'-bis(1-methylethyl)-, (2R)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **(-)-Apogossypol**
MF **C28 H30 O6**
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L17 ANSWER 2 OF 3 REGISTRY COPYRIGHT 2005 ACS on STN
RN 66389-74-0 REGISTRY
ED Entered STN: 16 Nov 1984
CN [2,2'-Binaphthalene]-1,1',6,6',7,7'-hexol, 3,3'-dimethyl-5,5'-bis(1-methylethyl)-, (2S)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **Apogossypol**
MF **C28 H30 O6**
LC STN Files: BEILSTEIN*, BIOSIS, CA, CAPLUS, CASREACT, DDFU, DRUGU, NAPRALERT, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)

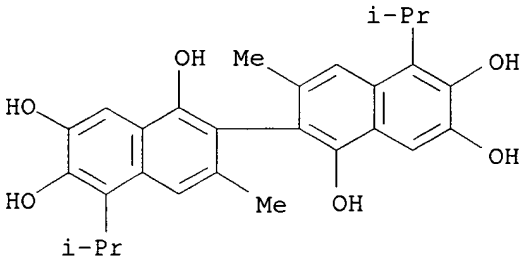


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

19 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
19 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L17 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2005 ACS on STN
RN 475-56-9 REGISTRY
ED Entered STN: 16 Nov 1984
CN [2,2'-Binaphthalene]-1,1',6,6',7,7'-hexol, 3,3'-dimethyl-5,5'-bis(1-methylethyl)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN [2,2'-Binaphthalene]-1,1',6,6',7,7'-hexol, 5,5'-diisopropyl-3,3'-dimethyl- (6CI, 8CI)

OTHER NAMES:
CN **(±)-Apogossypol**
FS 3D CONCORD
MF **C28 H30 O6**
LC STN Files: BEILSTEIN*, CA, CAOLD, CAPLUS, CASREACT, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

9 REFERENCES IN FILE CA (1907 TO DATE)
9 REFERENCES IN FILE CAPLUS (1907 TO DATE)
2 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=> FIL MEDL CAPL BIOSIS USPATFUL WPIDS

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	30.73	133.39

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-2.19

FILE 'MEDLINE' ENTERED AT 14:34:24 ON 29 OCT 2005

FILE 'CAPLUS' ENTERED AT 14:34:24 ON 29 OCT 2005
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FILE 'BIOSIS' ENTERED AT 14:34:24 ON 29 OCT 2005

FILE 'USPATFULL' ENTERED AT 14:34:24 ON 29 OCT 2005

FILE 'WPIDS' ENTERED AT 14:34:24 ON 29 OCT 2005

=> s l17
L18 36 L17

=> s (l8 or l11) and l18
2 FILES SEARCHED...
L19 10 (L8 OR L11) AND L18

=> dup rem l19
PROCESSING COMPLETED FOR L19
L20 7 DUP REM L19 (3 DUPLICATES REMOVED)

=> d ibib abs 5-7

L20 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2004:324496 CAPLUS
DOCUMENT NUMBER: 140:385353
TITLE: Breaking Down Tumor Defenses
AUTHOR(S): Hockenbery, David
CORPORATE SOURCE: Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, 98104, USA
SOURCE: Chemistry & Biology (2004), 11(4), 417-418
CODEN: CBOLE2; ISSN: 1074-5521
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. BCL-2 antiapoptotic proteins are considered ripe targets for anticancer drugs, yet only recently have small mol. inhibitors emerged. Beccatini and colleagues find a BCL-XL inhibitor in the guise of a familiar natural product, gossypol. An analog, apogossypol, is a relatively selective BCL-XL antagonist.
REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 2004:261470 CAPLUS
DOCUMENT NUMBER: 141:133679
TITLE: Rational design and real time, in-cell detection of the proapoptotic activity of a novel compound targeting Bcl-XL
AUTHOR(S): Becattini, Barbara; Kitada, Shinichi; Leone, Marilisa; Monosov, Edward; Chandler, Sharon; Zhai, Dayong; Kipps, Thomas J.; Reed, John C.; Pellecchia, Maurizio
CORPORATE SOURCE: The Burnham Institute, La Jolla, CA, 92037, USA
SOURCE: Chemistry & Biology (2004), 11(3), 389-395
CODEN: CBOLE2; ISSN: 1074-5521
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Antiapoptotic Bcl-2-family proteins Bcl-2 and Bcl-XL have been recently validated as drug discovery targets for **cancer**. Here, by using a combination of mol. modeling, NMR-based structural anal., fluorescence polarization assays, and cell-based assays, we have designed and characterized a novel proapoptotic compound targeting these proteins. Our compound, Apogossypol, is capable of binding and inhibiting Bcl-2 and Bcl-XL with high affinity and induces **apoptosis** of tumor cell lines. Mechanistic studies on the action of our compound were also performed via confocal microscopy that provided real-time detection of the interaction with Bcl-XL in intact cells. Finally, preliminary data on cells freshly isolated from patients affected by chronic lymphocytic leukemia strongly suggest potential applications of Bcl-2 antagonists as chemosensitizers in **cancer** therapy.
REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 7 OF 7 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:150189 BIOSIS
DOCUMENT NUMBER: PREV200400146881
TITLE: Rational design and real time in-cell detection of the pro-apoptotic activity of a novel compound targeting Bcl-2/Bcl-XL.
AUTHOR(S): Kitada, Shinichi [Reprint Author]; Becattini, Barbara [Reprint Author]; Leone, Marilisa [Reprint Author]; Monosov, Edward [Reprint Author]; Chandler, Sharon [Reprint Author]; Kipps, Thomas J.; Reed, John C. [Reprint Author];

Pellecchia, Maurizio [Reprint Author]
CORPORATE SOURCE: Burnham Institute, La Jolla, CA, USA
SOURCE: Blood, (November 16 2003) Vol. 102, No. 11, pp. 429a. print.
Meeting Info.: 45th Annual Meeting of the American Society of Hematology. San Diego, CA, USA. December 06-09, 2003. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 17 Mar 2004
Last Updated on STN: 17 Mar 2004

AB Altered expression of Bcl-2-family proteins plays a central role in **apoptosis** dysregulation in **cancer** and leukemia, promoting malignant cell expansion and contributing to chemoresistance. Recently, we discovered that Bcl-2 and Bcl-XL are targets of Gossypol, providing a potential molecular basis for the observed pro-apoptotic activity of this natural product and setting the stage for design of analogs with improved properties. The presence of two highly reactive aldehyde groups in Gossypol has created a major limitation to its therapeutic application. By using a combination of molecular modeling and structural biology techniques, we have designed and characterized a non-reactive compound analog (Apogossypol) lacking these aldehydes, and thus having better drug-like properties. To evaluate the inhibitory properties of Apogossypol for Bcl-XL we employed a competitive fluorescence polarization assay (FPA). Apogossypol was able to displace FITC-BH3 peptide from Bcl-XL with a Ki of 2.3 uM. To gain further insight into its mechanism of action we introduced mutations in the Bcl-XL protein by site directed mutagenesis (namely R139M), which was predicted on the basis of our model to abolish the interaction with Apogossypol. Low passage HeLa cells were transfected with plasmids encoding either wild-type Bcl-XL or R139M-Bcl-XL together with GFP-Bcl-Gs at a ratio of 10:1. After addition of Apogossypol (10 uM) to these cells, the change of the fluorescence intensity of GFP-Bcl-Gs tagged mitochondrial sites was quantified by live confocal time-lapse microscopy. In cells expressing wild-type Bcl-XL, mitochondrial fluorescence vanished within 2.5 minutes due to displacement by the compound. The same time, in the R139M-Bcl-XL transfected cells the decay of mitochondrial fluorescence was non-significant and comparable to the plain bleaching of wild type GFP. Finally, to further explore anticancer activities of Apogossypol, we tested its cytotoxicity against primary leukemic cells isolated from 12 different patients with chronic lymphocytic leukemia (CLL). Among them, 9 patients were untreated, while 3 patients had been treated with conventional chemotherapeutic agents, developing refractory disease (Rai stage 0:3 cases, Rai stage 1:2 cases and Rai stage 2:7 cases). Considerable variability in apoptotic responses to Apogossypol was observed, reflecting heterogeneity of this disease. Apogossypol induced **apoptosis** of 6 of the 9 treatment naive CLL samples, with an IC50 of 16 uM. However, when used in combination with a conventional cytotoxic anticancer drug, F-ara-A (the active metabolite of fludarabine), Apogossypol displayed synergistic effects in a subset of CLL patients, including 2 of the 3 fludarabine-refractory CLL specimens. Thus, while neither Apogossypol nor F-ara-A individually induced **apoptosis** of these CLL cells, **apoptosis** was induced in a dose-dependent manner by the combination of these agents. These data support the idea that Apogossypol and F-ara-A can act in a synergistic manner, whereby Apogossypol reverses chemoresistance through its effects on Bcl-2. Thus, taken together, our data strongly suggest that Apogossypol may be a useful therapeutic agent for the treatment of CLL and other malignancies linked to over-expression of Bcl-2 or Bcl-XL, where chemorefractory states represent a barrier to successful eradication of **cancer**.

```
=> s endometriosis or restenosis
L21      78987 ENDOMETRIOSIS OR RESTENOSIS

=> s l18 and l21
L22          0 L18 AND L21

=> log h
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                      19.79     153.18

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                         ENTRY    SESSION
CA SUBSCRIBER PRICE                                      -1.46      -3.65

 SESSION WILL BE HELD FOR 60 MINUTES
STN INTERNATIONAL SESSION SUSPENDED AT 14:37:37 ON 29 OCT 2005

Connecting via Winsock to STN



Welcome to STN International!  Enter x:x

LOGINID:ssspta1617srh

PASSWORD:
 * * * * * * RECONNECTED TO STN INTERNATIONAL * * * * * *
SESSION RESUMED IN FILE 'MEDLINE, CAPLUS, BIOSIS, USPATFULL, WPIDS'
AT 15:00:08 ON 29 OCT 2005
FILE 'MEDLINE' ENTERED AT 15:00:08 ON 29 OCT 2005
FILE 'CAPLUS' ENTERED AT 15:00:08 ON 29 OCT 2005
COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY (ACS)
FILE 'BIOSIS' ENTERED AT 15:00:08 ON 29 OCT 2005
Copyright (c) 2005 The Thomson Corporation
FILE 'USPATFULL' ENTERED AT 15:00:08 ON 29 OCT 2005
CA INDEXING COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY (ACS)
FILE 'WPIDS' ENTERED AT 15:00:08 ON 29 OCT 2005
COPYRIGHT (C) 2005 THE THOMSON CORPORATION

COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                      19.79     153.18

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
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CA SUBSCRIBER PRICE                                      -1.46      -3.65

=> fil reg
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
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FULL ESTIMATED COST                                      19.79     153.18

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
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CA SUBSCRIBER PRICE                                      -1.46      -3.65

FILE 'REGISTRY' ENTERED AT 15:00:13 ON 29 OCT 2005
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```

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 27 OCT 2005 HIGHEST RN 866318-76-5
DICTIONARY FILE UPDATES: 27 OCT 2005 HIGHEST RN 866318-76-5

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

Please note that search-term pricing does apply when conducting SmartSELECT searches.

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**********************************************************************
*                                                                    *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,   *
* effective March 20, 2005.  A new display format, IDERL, is now    *
* available and contains the CA role and document type information. *
*                                                                    *
**********************************************************************
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Structure search iteration limits have been increased. See HELP SLIMITS for details.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

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=> s ethyl gossypol
       7011832 ETHYL
            13 ETHYLS
       7011832 ETHYL
                  (ETHYL OR ETHYLS)
            91 GOSSYPOL
L23          2 ETHYL GOSSYPOL
                  (ETHYL(W)GOSSYPOL)

=> d tot

L23  ANSWER 1 OF 2  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   784206-40-2  REGISTRY
ED   Entered STN:  19 Nov 2004
CN   [2,2'-Binaphthalene]-8,8'-dicarboxaldehyde, 5,5'-diethyl-1,1',6,6',7,7'-
     hexahydroxy-3,3'-dimethyl-, (2S)- (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   (+)-Ethyl gossypol
MF   C28 H26 O8
SR   CA
LC   STN Files:   CA, CAPLUS, TOXCENTER, USPATFULL
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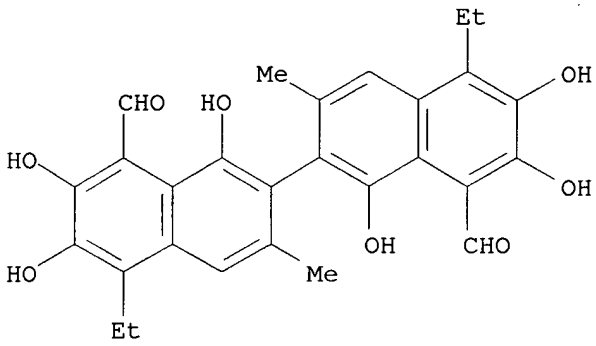
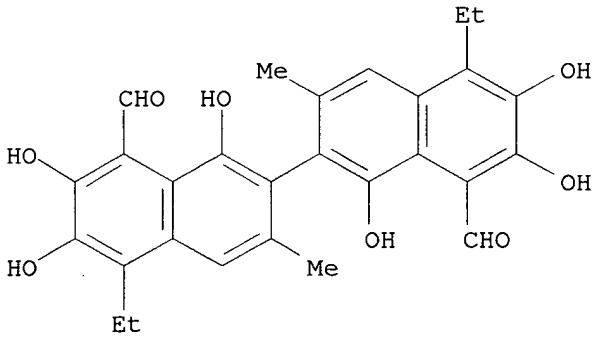


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L23 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2005 ACS on STN
RN 784206-39-9 REGISTRY
ED Entered STN: 19 Nov 2004
CN [2,2'-Binaphthalene]-8,8'-dicarboxaldehyde, 5,5'-diethyl-1,1',6,6',7,7'-hexahydroxy-3,3'-dimethyl-, (2R)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **(-)-Ethyl gossypol**
MF C28 H26 O8
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> FIL MEDL CAPL BIOSIS USPATFUL WPIDS

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	13.31	166.49

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-3.65

FILE 'MEDLINE' ENTERED AT 15:00:31 ON 29 OCT 2005

FILE 'CAPLUS' ENTERED AT 15:00:31 ON 29 OCT 2005
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FILE 'USPATFULL' ENTERED AT 15:00:31 ON 29 OCT 2005
CA INDEXING COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'WPIDS' ENTERED AT 15:00:31 ON 29 OCT 2005
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=> s l23
L24 4 L23

=> dup rem l24
PROCESSING COMPLETED FOR L24
L25 3 DUP REM L24 (1 DUPLICATE REMOVED)

=> d ibib abs tot

L25 ANSWER 1 OF 3 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2005-564053 [57] WPIDS
CROSS REFERENCE: 2003-140460 [13]
DOC. NO. CPI: C2005-170457
TITLE: Treating, ameliorating or preventing hyperproliferative disease e.g., cancer in subject, involves administering gossypol compound and anticancer agent to subject, or administering gossypol compound and subjecting subject to radiation.
DERWENT CLASS: B04 B05
INVENTOR(S): WANG, S; YANG, D
PATENT ASSIGNEE(S): (GEOU) UNIV GEORGETOWN MEDICAL CENT; (UNMI) UNIV MICHIGAN
COUNTRY COUNT: 108
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2005069771	A2	20050804	(200557)*	EN	262

RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2005069771	A2	WO 2004-US40553	20041206

PRIORITY APPLN. INFO: US 2003-729156 20031205
AN 2005-564053 [57] WPIDS
CR 2003-140460 [13]
AB WO2005069771 A UPAB: 20050907

NOVELTY - Treating, ameliorating or preventing (M1) a hyperproliferative disease in a subject, involves administering to the subject a gossypol compound and one or more second agent chosen from an anticancer agent and radiation, where the combination of (plus or minus)-gossypol, heat, and radiation is not administered.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a pharmaceutical composition (PC) comprising a gossypol compound and one or more anticancer agents; and

(2) a kit comprising a gossypol compound, one or more anticancer agents, and instructions for administering the gossypol compound and the anticancer agents to a subject.

ACTIVITY - Cytostatic; Anti-HIV; Vasotropic; Antiinflammatory; Antibacterial; Fungicide; Virucide.

MECHANISM OF ACTION - Antagonist of Bcl-2 family proteins; Induces apoptosis; Inhibits cell proliferation. In vivo analysis of gossypol compounds in combination with radiation therapy in inhibiting cell proliferation was carried out in PC-3 xenograft mouse model as follows. The xenograft mice (25) were divided into 5 groups. Group 1 (vehicle control) mice were orally administered with alcohol (10%), daily, Group 2 (radiation only) mice were subjected to radiation (2 Gy) 5 times/week for 2 weeks and orally administered daily with alcohol (10%), Group 3 (radiation plus gossypol) mice were subjected to radiation (2 Gy) 5 times/week for 3 weeks and orally administered daily with (-)-gossypol (10 mg/kg) every day for 4 weeks, Group 4 (gossypol only) mice were orally administered daily with (-)-gossypol (10 mg/kg) every day for 4 weeks, and Group 5 (control) mice were not subjected to treatment. During the treatment course, tumor sizes and animal weights were measured 3 times per/week for each animal. Treatment with (-)-gossypol alone or with radiation therapy alone had minimal antitumor effect. Results showed that there was more than 90% inhibition in tumor cell growth in animals receiving radiation therapy in combination with gossypol as compared to the group controls.

USE - (M1) is useful for treating, ameliorating or preventing a hyperproliferative disease in a subject, where the subject is a human. The disease is neoplastic disease. The hyperproliferative disease is cancer, preferably breast cancer, prostate cancer, pancreatic cancer, colon cancer, lung cancer, lymphoma, melanoma or head-neck cancer. The cancer is metastatic or is a tumor, where the treatment or amelioration results in regression of the tumor. The hyperproliferative disease is associated with overexpression of a Bcl-2 family member protein, where the Bcl-2 family protein is Bcl-2, Bcl-XL, Mcl-1, A1/BFL-1, BOO-DIVA, Bcl-w, Bcl-6, Bcl-8 or Bcl-y. The cancer is resistant to anticancer agent or radiation therapy (all claimed). PC is useful for treating hyperproliferative disease, tumor such as Wilm's tumor, metastatic cancer, cervical carcinoma, testicular carcinoma, genitourinary carcinoma, thyroid carcinoma, Hodgkin's disease, non-Hodgkin's sarcoma, etc. PC is useful for treating infections (e.g., bacterial, viral, fungal and mycoplasma infections), AIDS, inflammatory disease, vascular diseases, etc. PC is useful for preventing the onset or spread of neoplastic disease, for treating diseased cells, tissues, organs or pathological conditions and/or disease states in a subject, and for modulating cell division in a tissue.

ADVANTAGE - PC is less toxic and more tolerable.

DESCRIPTION OF DRAWING(S) - The figure is a graph representing the tumor size in PC-3 xenograft model mice subjected to radiation and/or gossypol treatments.

Dwg.36/46

L25 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 1

ACCESSION NUMBER: 2004:907153 CAPLUS

DOCUMENT NUMBER: 141:388644

TITLE: Gossypol compound antagonists of Bcl-2 family proteins, and use with with other therapeutic means in

the treatment of neoplastic and other diseases
INVENTOR(S): Wang, Shaomeng; Yang, Dajun
PATENT ASSIGNEE(S): The Regents of the University of Michigan, USA; Georgetown University
SOURCE: U.S. Pat. Appl. Publ., 143 pp., Cont.-in-part of U.S. Ser. No. 158,769.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004214902	A1	20041028	US 2003-729156	20031205
WO 2002097053	A2	20021205	WO 2002-US17206	20020530
WO 2002097053	A3	20040910		
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US 2003008924	A1	20030109	US 2002-158769	20020530
WO 2005069771	A2	20050804	WO 2004-US40553	20041206
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.:		
US 2001-293983P	P	20010530
US 2002-158769	A2	20020530
WO 2002-US17206	A2	20020530
US 2003-729156	A	20031205

AB The invention relates to naturally occurring and chemical synthesized small mol. antagonists of Bcl-2 family proteins. In particular, the invention provides gossypol compds. (e.g., isomers, enantiomers, racemic compds., metabolites, derivs., pharmaceutically acceptable salts, in combination with acids or bases, and the like) and methods of using these compds. as antagonists of the anti-apoptotic effects of Bcl-2 family member proteins (e.g., Bcl-2, Bcl-XL, and the like). The invention also provides compns. comprising gossypol compds. and optionally one or more addnl. therapeutic agents (e.g., anticancer/chemotherapeutic agents). The invention also provides methods for treating diseases and pathologies (e.g., neoplastic diseases) comprising administering a composition comprising gossypol compds. and optionally one or more addnl. therapeutic agents (e.g., anticancer/chemotherapeutic agents) and/or techniques (e.g., radiation therapies, surgical interventions, and the like) to a subject or in vitro cells, tissues, and organs. Preparation of gossypolone is included.

L25 ANSWER 3 OF 3 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-140460 [13] WPIDS
CROSS REFERENCE: 2005-564053 [57]

DOC. NO. CPI: C2003-035675
TITLE: Modulating apoptosis or cell division in a tissue, treating a subject overexpressing Bcl-2 family protein, and treating cancer in a subject, by administering gossypol compound to the cell, tissue or subject.
DERWENT CLASS: B04 D16
INVENTOR(S): WANG, S; YANG, D
PATENT ASSIGNEE(S): (UNMI) UNIV MICHIGAN; (GEOU) UNIV GEORGETOWN MEDICAL CENT; (GEOU) UNIV GEORGETOWN
COUNTRY COUNT: 101
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002097053	A2	20021205	(200313)*	EN	96
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW					
US 2003008924	A1	20030109	(200313)		
NO 2003005301	A	20040130	(200419)		
AU 2002305769	A1	20021209	(200452)		
US 2004214902	A1	20041028	(200471)		
EP 1474121	A2	20041110	(200473)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					
KR 2004108528	A	20041224	(200528)		
JP 2005515158	W	20050526	(200535)		55
CN 1589135	A	20050302	(200537)		

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 2002097053	A2		WO 2002-US17206	20020530
US 2003008924	A1	Provisional	US 2001-293983P	20010530
			US 2002-158769	20020530
NO 2003005301	A		WO 2002-US17206	20020530
			NO 2003-5301	20031128
AU 2002305769	A1		AU 2002-305769	20020530
US 2004214902	A1	Provisional	US 2001-293983P	20010530
		CIP of	US 2002-158769	20020530
		CIP of	WO 2002-US17206	20020530
			US 2003-729156	20031205
EP 1474121	A2		EP 2002-734614	20020530
			WO 2002-US17206	20020530
KR 2004108528	A		KR 2003-715683	20031129
JP 2005515158	W		WO 2002-US17206	20020530
			JP 2003-500222	20020530
CN 1589135	A		CN 2002-813299	20020530

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2002305769	A1	Based on	WO 2002097053
EP 1474121	A2	Based on	WO 2002097053
JP 2005515158	W	Based on	WO 2002097053

PRIORITY APPLN. INFO: US 2002-158769 20020530; US

2001-293983P 20010530; US
2003-729156 20031205

AN 2003-140460 [13] WPIDS
CR 2005-564053 [57]
AB WO 200297053 A UPAB: 20050907

NOVELTY - Modulating (M1) apoptosis in a cell, modulating cell division in a tissue, treating a subject overexpressing Bcl-2 family protein, and treating cancer in a subject, comprising administering gossypol compound (I) to the cell, tissue or subject, is new.

DETAILED DESCRIPTION - Modulating (M1) apoptosis in a cell, modulating cell division in a tissue, treating a subject overexpressing Bcl-2 family protein, and treating cancer in a subject, comprising:

(a) modulating apoptosis, by treating a cell that overexpresses Bcl-2 family protein, with an effective amount of (I);

(b) modulating cell division in a tissue, by treating a tissue that overexpresses Bcl-2 family protein, with effective amounts of (I) and an anticancer agent;

(c) treating a subject overexpressing a Bcl-2 family protein, by administering (I) and optionally an anticancer agent, to the subject; and

(d) treating cancer in a subject, by administering an effective amount (I) and optionally an anticancer agent, to a patient having a condition characterized by overexpression of Bcl-2 family protein, to a patient having cancer characterized by overexpression of Bcl-2 family protein, or to a patient characterized by resistance to cancer therapies, where the dose of (I) and anticancer agent is sufficient to reduce the overexpression of the Bcl-2 protein.

INDEPENDENT CLAIMS are also included for the following:

(1) a pharmaceutical composition (PC) comprising (I) and instructions for administering (I) to a subject characterized by overexpression of a Bcl-2 family protein or by resistance to a cancer therapy; and

(2) screening (M2) a gossypol compound and a test compound, by contacting a first group of cells with (I) and a test compound, and observing the effects of contacting the first group of cells with (I) and the test compound.

ACTIVITY - Cytostatic; Anti-HIV; Antibacterial; Virucide; Fungicide.

MECHANISM OF ACTION - Antagonists Bcl-2 family proteins; Modulator of apoptosis and cell division; Inhibitor of tumor growth.

The MDA-MB-231 breast cancer cell line has a high level of both Bcl-2 and Bcl-XL expression. The ability of gossypol to inhibit MDA-MB-231 cell growth was tested in a 5 day 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay. Gossypol was shown to inhibit MDA-MB-231 cell growth with an IC50 value of 2.0 micro M. Treatment of MDA-MB-231 cancer cells with gossypol induced apoptosis in the cancer cells, but not in normal WI-38 fibroblast cells. In other tests, gossypol was shown to induce apoptosis in T-47D breast cancer cells that have high levels of Bcl-XL expression, but low levels of Bcl-2 expression. It was also found that gossypol induces apoptosis in other cancer cell lines with high Bcl-XL such as, human colon cancer cell line HT-29, but not in cancer cell lines with low Bcl-2 and low Bcl-XL expression, such as prostate cancer cell line DU-145.

USE - M1 or PC is useful for modulating apoptosis in a diseased cell (e.g. hyperproliferative disease, cancer, AIDS, degenerative condition, vascular disease and infection by pathogen e.g. bacteria, fungi or virus), modulating cell division in a tissue, treating a subject having a condition characterized by overexpression of Bcl-2 family protein, and treating cancer in a subject, where the cancer includes cancer of breast, prostate, skin, pancreas, colon, ovary, brain, liver, bladder, non-small lung or cervix, or melanoma, carcinoma, myeloma, adrenal carcinoma, lymphoma, leukemia, neuroblastoma, glioblastoma and head-neck cancer. The cancer may be metastatic or resistant to cancer therapy including chemotherapy, radiation therapy or hormone treatment. (All claimed.)

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	17.25	183.74

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-0.73	-4.38

SESSION WILL BE HELD FOR 60 MINUTES
STN INTERNATIONAL SESSION SUSPENDED AT 15:02:13 ON 29 OCT 2005

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	1	ethyl adj apogossypol	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2005/10/29 14:21
L2	186	514/682.ccls.	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2005/10/29 14:21
L3	536	gossypol	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2005/10/29 14:21
L4	7	gossypolone	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2005/10/29 14:21
L5	112	gossypol and cancer	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2005/10/29 14:21
L6	2	"ethyl gossypol" and cancer	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2005/10/29 14:21
L7	2	"5385936".pn.	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2005/10/29 14:21
L8	4	apogossypol and cancer	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2005/10/29 14:21
L9	5	apogossypol	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2005/10/29 14:21

L10	3	hemigossypolone	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2005/10/29 14:21
S1	536	gossypol	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2005/10/26 17:40
S2	7	gossypolone	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2005/10/26 17:40
S3	112	gossypol and cancer	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2005/10/28 16:34
S4	2	"ethyl gossypol" and cancer	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2005/10/28 10:48
S5	2	"5385936".pn.	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2005/10/28 10:48
S6	4	apogossypol and cancer	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2005/10/28 16:34
S7	5	apogossypol	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2005/10/29 14:15
S8	3	hemigossypolone	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2005/10/29 14:02